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PHASE-TRANSFER CATALYSIS AS A TOOL FOR BUILDING QUATERNARY STEREOCENTERS

Master's thesis for the degree of Master of Science in Technology submitted for inspection, Espoo, 29 September, 2015.

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Abstract

Enantioselective Michael additions of α-substituted phenylpropanoates to acrylonitriles as well as enantioselective Michael additions of substituted benzyl cyanides to acrylates were attempted using phase-transfer catalysts. Application of dimeric *Cinchona* alkaloid derived catalysts (5 mol-%) in the Michael addition of α-methylbenzyl cyanide to ethyl acrylate under mild reaction conditions provided the product with up to 28% enantiomeric excess. A number of *Cinchona* alkaloid derived catalysts were evaluated as well as other phase-transfer catalysts such as chiral tetraaminophosphonium salts of Ooi and co-workers and the pentanidium salt of Tan and co-workers. However, reactions catalysed with these catalysts gave enantioselectivities below 28% ee or near racemic. In an attempt to increase the enantioselectivity of the reaction of the α-methylbenzyl cyanide to ethyl acrylate, more steric bulk was added to the benzyl cyanide by using α-isopropylbenzyl cyanide instead of the α-methylbenzyl cyanide. Application of *N*-benzylcinchonidinium bromide (5 mol-%) in the Michael addition of α-isopropylbenzyl cyanide to ethyl acrylate under mild reaction conditions provided the product with a enantiomeric excess of up to 30%.

Keywords Phase-transfer catalysis, Cinchona alkaloid, asymmetric alkylation, Michael addition, substituted benzyl cyanides

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Sammandrag

Enantioselektiva Michael additionsreaktioner av α-substituerade fenylpropanoater till akrylnitriler samt enantioselektiva Michael additionsreaktioner av bensyl cyanider till akrylater utfördes med hjälp av fas-överförings katalysatorer. Användning av dimeriska *Cinchona*-alkaloid derivat som katalysatorer (5 mol-%) i Michael additionsreaktionen av α-metylbensyl cyanid till etyl akrylat under milda reaktionsbetingelser gav produkten med ett enantiomeriskt överskott upp till 28% ee. Ett antal *Cinchona*-alkaloid härledda katalysatorer utvärderades liksom även andra katalysatorer så som Ooi och kollegers kirala tetraaminofosfonium salter och pentanidium saltet utvecklat av Tan och medarbetare. Olyckligtvis var produkterna som hade katalyserats med dessa under 28% ee eller nära till rasemiska.

I ett försök att förbättra enantioselektiviteten i additionsreaktionen av α-metylbensyl cyaniden till etyl akrylat, ersattes α-metylbensyl cyaniden med en större och därmed mera sterisk bensyl cyanid, en α-isopropylbensyl cyanid. Användningen av *N*-bensylcinkonidinium bromid (5 mol-%) i Michael additionsreaktionen av α-isopropylbensyl cyanid till etylakrylat under milda reaktionsbetingelser gav produkten med ett enantiomerisk överskott på upp till 30% ee.

Nyckelord Fas-överförings katalys, *Cinchona* alkaloid, asymmetrisk alkylering, Michael additionsreaktion

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Espoo September 29th, 2015

Antonia Högnäsbacka

Symbols used in text

J	NMR coupling constant, Hz
δ	NMR chemical shift, ppm
pK_a	The acid dissociation constant at logarithmic scale
Q^+	The paring cation in phase-transfer catalysts
En^-	Enolate

Abbreviations used in text

BTEA	Benzyltriethylammonium
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
EWG	Electron withdrawing group
HRMS	High-resolution mass spectrometry
NMR	Nuclear magnetic resonance
THF	Tetrahydrofuran
UPLC-MS	Ultra performance liquid chromatography combined with mass spectrometry
LogD	The distribution coefficient at logarithmic scale
LogP	The partition coefficient at logarithmic scale

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1. Introduction

In 1971 Charles M. Starks first coined the term “phase-transfer catalysis”. This term described a solution to the heterogeneity problem that arises when substances of a reaction are in different phases of the reaction mixture. Traditionally this problem was solved by issuing an appropriate mutual solvent, but by adding a small quantity of an agent which transfers one reactant across the interface into the other, the reaction can proceed smoothly even in the case of heterogeneous phase systems. Starks found that organic-soluble quaternary ammonium or phosphonium cations, Q^+, were suitable agents for the transport of anions from the aqueous phase to the organic phase (Figure 1). [1]

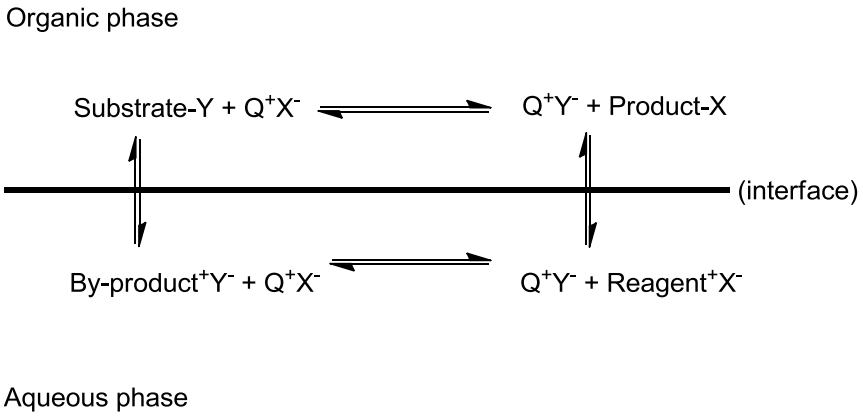
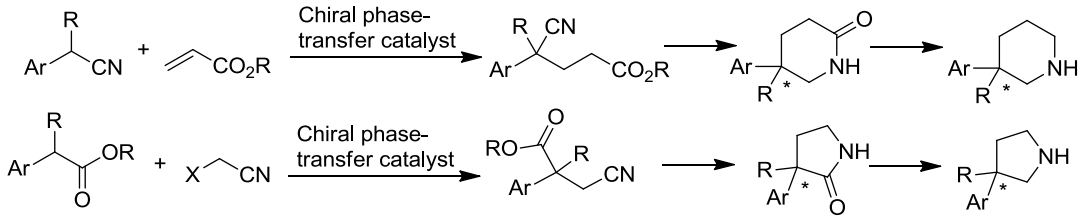


Figure 1. Illustration of phase-transfer catalysis (Starks extraction mechanism).

The focus in phase-transfer catalysis has mainly been on structures such as protected prochiral glycine derivatives and malonates, and less attention has been paid to substrates with a higher pK_a [2]. To the best of my knowledge the type of reaction which is aimed for in this thesis (Scheme 1) has only been successfully performed chirally by using chiral crown ethers [3]. Since all research that addresses this type of phase-transfer catalysis is from the beginning of the 1980’s to early 1990’s, it would be preferable to evaluate the categories of catalysts that have been developed since then.



Scheme 1. Generating new stereocenters via chiral phase-transfer catalysis.

The method that is aimed to be developed could possibly enable the synthesis of the neurokinin 3 receptor antagonist Osanetant, the L-type calcium channel blocker (*S*)-Verapamil and the opioid analgesic Profadol (Figure 2).

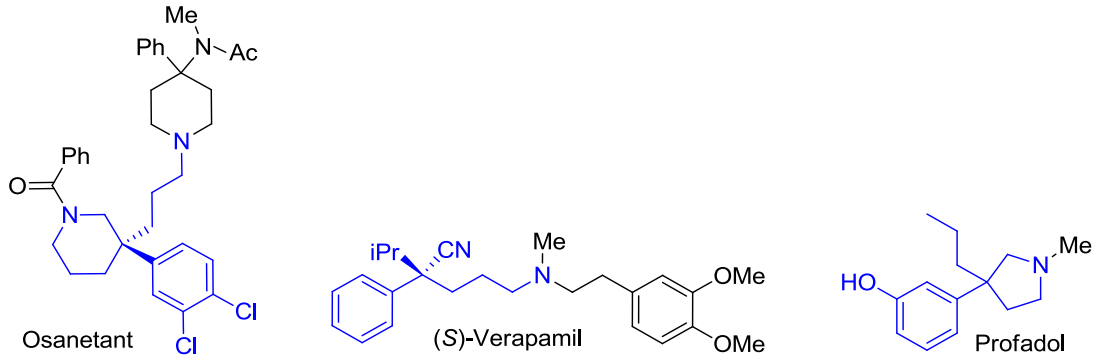


Figure 2. The structure of possible structures containing the stereocenter aimed for.

This thesis aims to develop a method generating new stereocenters via chiral phase-transfer catalysis. This involves choosing the starting material, finding the optimal catalyst and optimization of reaction conditions such as solvent, temperature and base.

This thesis is divided into six chapters. Chapter 2 gives an overview of catalysts used for phase-transfer catalysis while chapter 3 will analyze phase-transfer catalyzed Michael additions. Chapters 4 and 5 summarize the experimental part of the thesis.

2. Evolution of phase-transfer catalysts

Though Stark was the first to coin the term “phase-transfer catalysis”, he was not alone in setting the foundation for the method. Reports that some quaternary compounds assist in carbanion reactions in the presence of aqueous alkali hydroxides in two-phase systems had appeared already in the early 50’s. The foundations for phase-transfer catalysis were essentially a combination of the work started by Makosza in the mid-60s, and the input by Brändström and Stark in the 70’s. [4]

Two mechanisms have been suggested for hydroxide-initiated phase-transfer-catalysis to explain the activity of the catalyst. The first mechanism is the one mentioned in the introduction, namely the extraction mechanism suggested by Stark [1] (Figure 3, left) and the second one is the interfacial mechanism proposed by Makosza [5] (Figure 3, right). The extraction mechanism suggests that a quaternary ammonium species (Q^+) acts to transfer the hydroxide ion to the organic phase to generate the ammonium enolate (Q^+En^-) [1]. In the interfacial mechanism it is suggested that the enolate is formed at the interfacial region between the organic phase and the aqueous phase by the action of the hydroxide ion. The newly formed carbanion will subsequently form an organic phase soluble ion-pair with the cation supplied by catalyst. [5]

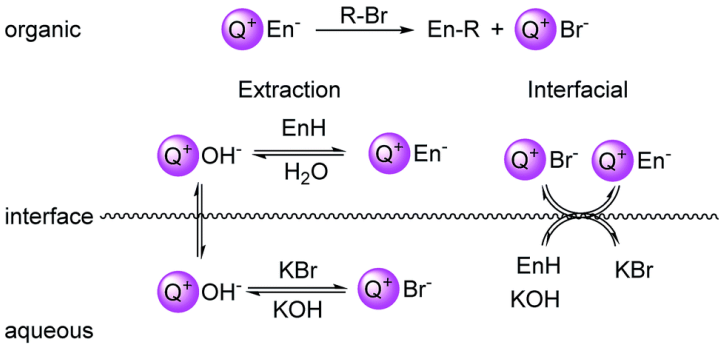
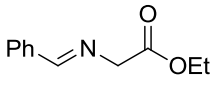
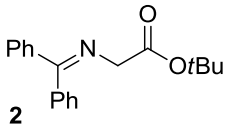
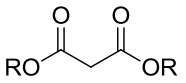
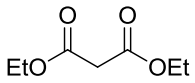
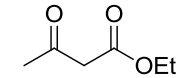
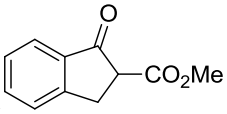
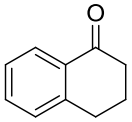
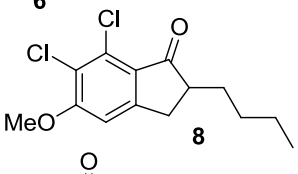
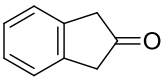
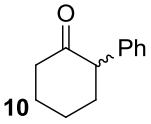
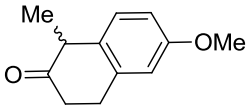
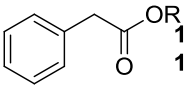
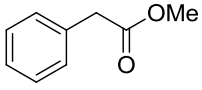
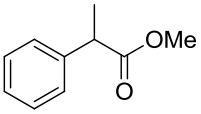
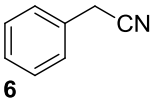
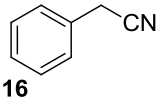
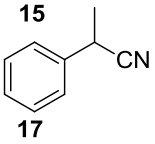
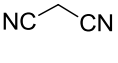
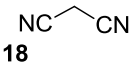
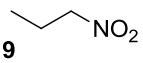
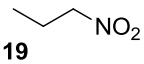


Figure 3. Left: the extraction mechanism; Right: the interfacial mechanism. En^- = enolate [6]

Numerous kinetic studies have supported both of these mechanisms, depending on reaction conditions. A general guideline is that phase-transfer catalyzed reactions of carbon acids follow the interfacial mechanism when the carbon acid is within a pK_a range of 18 to 25. [6] Bordwell’s collection of pK_a values for substances similar to the starting materials in this literary review is provided below (Table 1) [7].

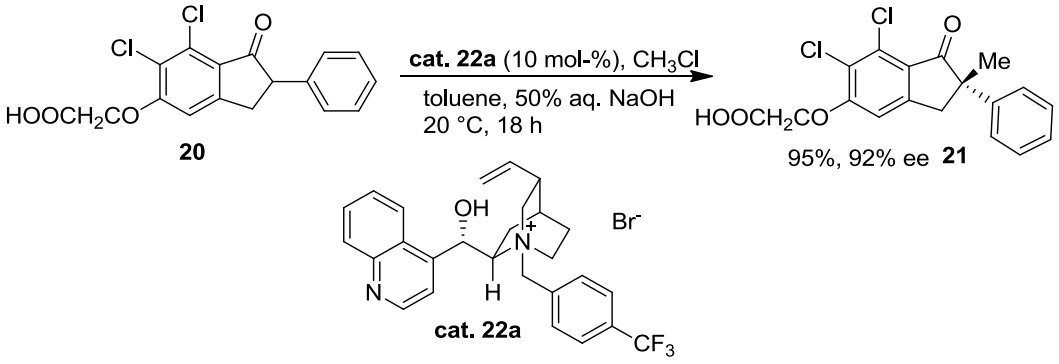
Table 1. Bordwell pKa values (acidity in DMSO).

Structure	pK_a	Structures found in the literary review of this thesis
 **1**	19.5	 **2**
 **3** R = Me 15.9 **4** R = Et 16.4		 **4**
 **5**	14.2	 **6**
 **7**	24.7	 **8**
 **9**	16.9	 **10**
		 **11**
 **12** R = Et: 22.7 **13** R = tBu: 23.6		 **14**  **15**
 **16**	21.9	 **16**  **17**
 **18**	11.1	 **18**
 **19**	17.0	 **19**

2.1. *Cinchona* alkaloid derived catalysts

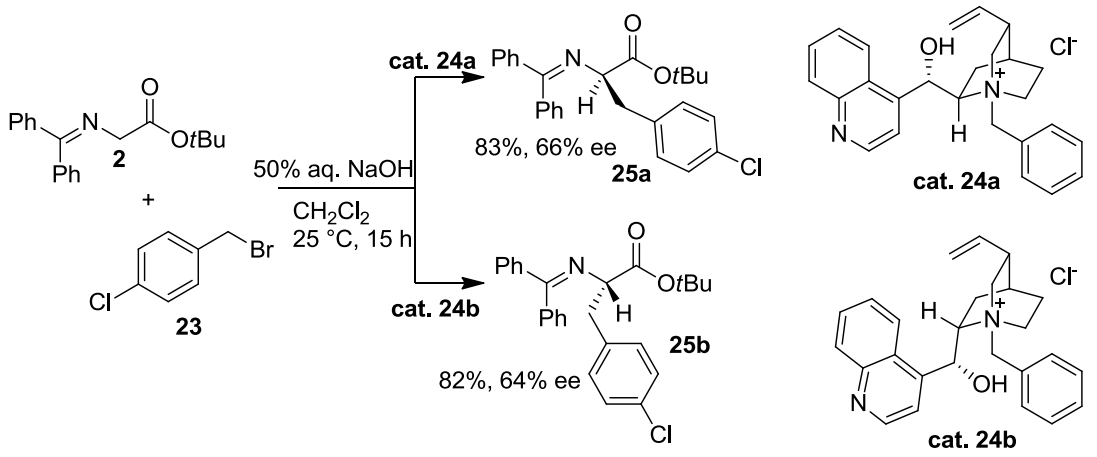
In 1984 the discovery by a Merck research group created a noticeably boost in the field of phase-transfer catalysis. Merck researchers succeeded in executing an enantioselective alkylation by using a chiral catalyst in their asymmetric synthesis of

uricosuric (+)-indacrinone (Scheme 2). The aforementioned chiral catalyst used in this reaction was *N*-(*p*-trifluoromethyl)benzylcinchoninium bromide (catalyst **22a**) [8, 2].



Scheme 2. The Merck group's enantioselective alkylation synthesis.

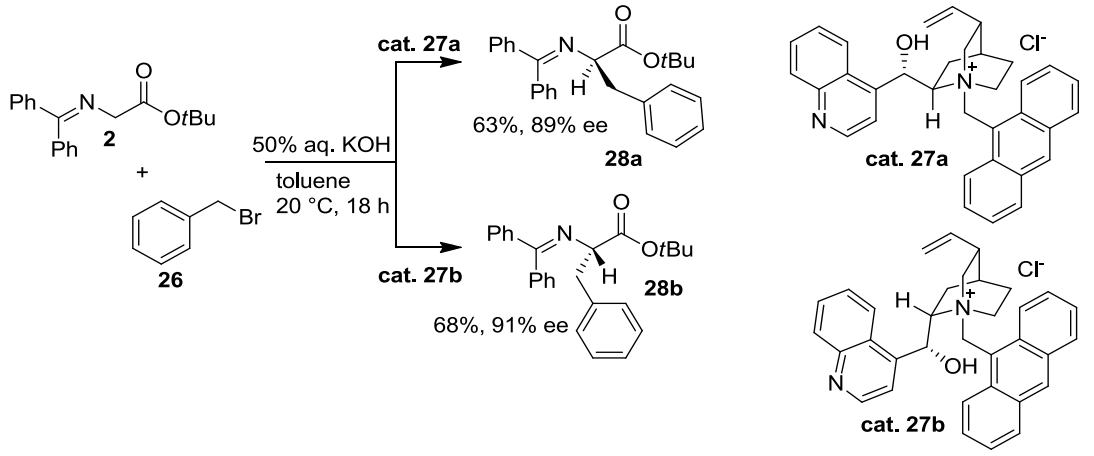
It has been found that two characteristics benefit the paring cation (Q^+) the most; being organically soluble and having a large ionic radius, thus improving the displacement rate [1]. This is also why ammonium and phosphonium salts have become so popular in phase-transfer catalysis. Especially in the chiral catalyst array, catalysts derived from *Chinchona* alkaloids have been popular study targets. [2] Other than having the beneficial characteristics of a good phase-transfer catalyst, they are also usually inexpensive and the tertiary amine and/or the secondary alcohol in the catalyst can be modified to bring more bulk or electronic effect to the catalyst. In addition, both enantiomers can potentially be prepared by interchanging the catalyst from a cinchonine-based to a cinchonidine-based catalyst series. This property was observed for the first time in a study performed by O'Donnell and co-workers in 1989, when catalysts **24a** and **24b** were discovered to be enantio-complimentary in the sense that they led to selectivity for the opposite enantiomers of the product. The chiral phase-transfer catalysts in question were used for the first asymmetric alkylation of glycine imine ester **2** (Scheme 3). The reactions were successfully carried out with *N*-benzyl derivatives of the *Cinchona* alkaloids cinchonidine and cinchonine as phase-transfer catalysts. [9]



Scheme 3. The asymmetric synthesis path of O'Donnell and co-workers.

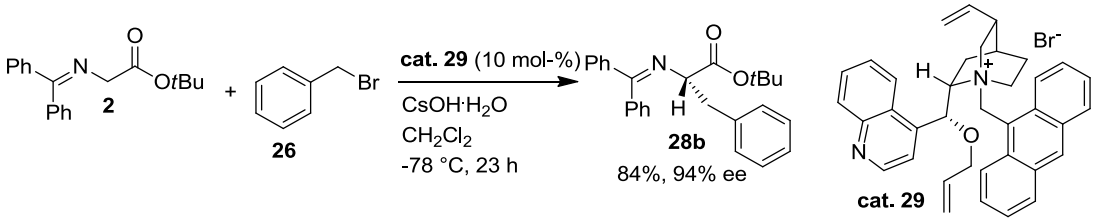
A significant challenge in the alkylation of a prochiral substrate is to obtain a product that has only been alkylated once. In the reaction above, the substrate is only alkylated once because of the sufficiently lower acidity of the remaining α-proton. As will be discernable in the literary review part of this thesis, protected prochiral glycine derivatives have been very popular substrates in phase-transfer catalysis. Together with a chiral catalyst, protected prochiral glycine derivatives create an attractive method for the preparation of optically active α-amino acids. In the above mentioned study, O'Donnell and co-workers found that the *tert*-butyl ester Schiff base **2** gave the best results in the substrate scope [9].

The next significant progress in the development of *Cinchona* alkaloid derived phase-transfer catalysis was the creation of a new generation of *Cinchona* derived catalysts. Lygo and co-workers created *N*-anthracenylmethylammonium salts **3a** and **3b** in 1997. They utilized the new catalysts in the same reaction as O'Donnell, with slight variation in the reaction conditions (Scheme 4). [10]



Scheme 4. The asymmetric synthesis path of Lygo and co-workers.

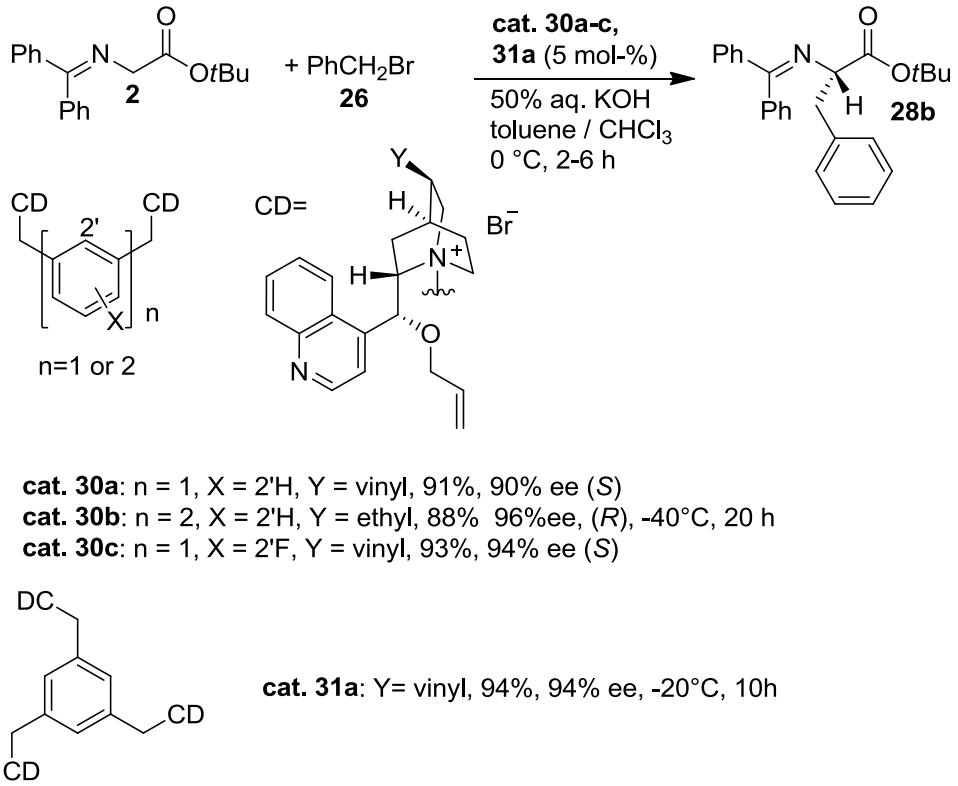
At the same time as Lygo and co-workers reported their *N*-anthracenyl-methylammonium salts, Corey and co-workers introduced another catalyst in this category. However, for their synthesis they used caesium hydroxide monohydrate as the base to minimize the amount of water in the organic phase and allow the use of temperatures lower than those possible with a 50% aqueous NaOH or KOH solution (Scheme 5) [11]. In connection to their previous study on bis-*Cinchona* alkaloid catalysts they found that when attached to a quaternary ammonium structure with a defined geometry, like in the case of cinchonidine, the 9-anthracenylmethyl group blocks the second tetrahedral face of the positively charged nitrogen [12].



Scheme 5. The asymmetric synthesis path of Corey and co-workers.

During the development of the asymmetric Sharpless dihydroxylation, it was discovered that ligands with two independent *Cinchona* alkaloid units attached to heterocyclic spacers (for example a phthalazine core or diphenylpyrimidine core [13]) led to considerable enhancement in enantioselectivity and increased the substrate scope. [14] Inspired by the discovery of the positive influence of a bulky subunit such as the anthracenyl-group and the dimerization effect in the asymmetric Sharpless dihydroxylation, Jew, Park and co-workers decided to study the effect of dimeric

catalysts. The most successful catalysts are gathered below. (Scheme 6) [15, 16, 17, 18]



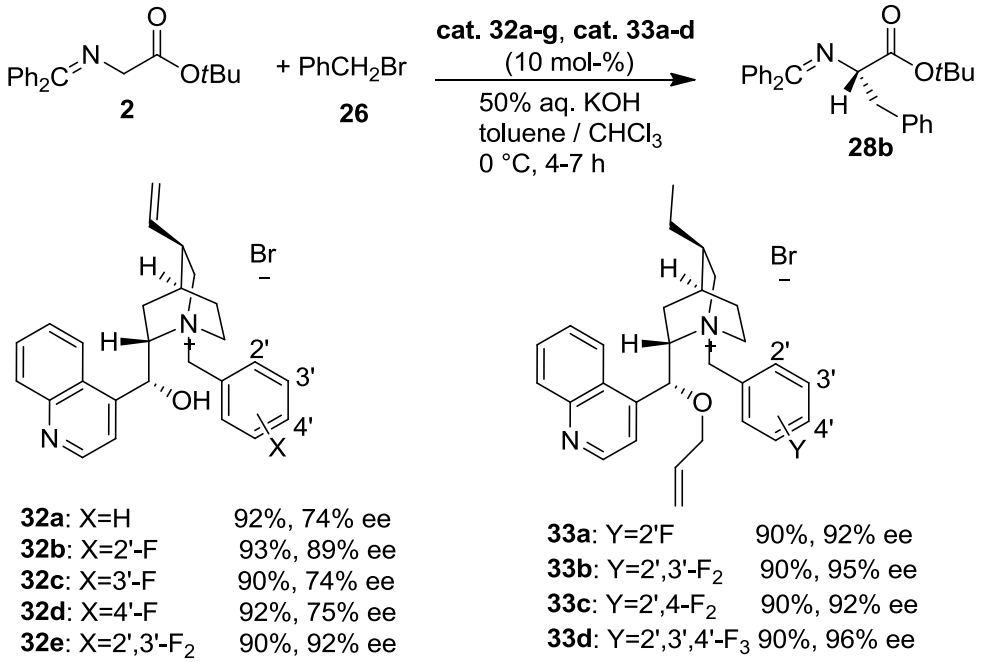
cat. 30a: n = 1, X = 2'H, Y = vinyl, 91%, 90% ee (*S*)
cat. 30b: n = 2, X = 2'H, Y = ethyl, 88% 96%ee, (*R*), -40°C, 20 h
cat. 30c: n = 1, X = 2'F, Y = vinyl, 93%, 94% ee (*S*)

cat. 31a: Y= vinyl, 94%, 94% ee, -20°C, 10h

Scheme 6. Dimeric catalysts created by Jew, Park and co-workers.

Other groups have also shown interest for the effect on reactions catalyzed by dimeric catalysts, such as Nájera and co-workers, but since the catalysts they studied (dimethylanthracenyl bridged dimeric compounds) are not utilized in this thesis, they will not be covered in this literature review part of the thesis.

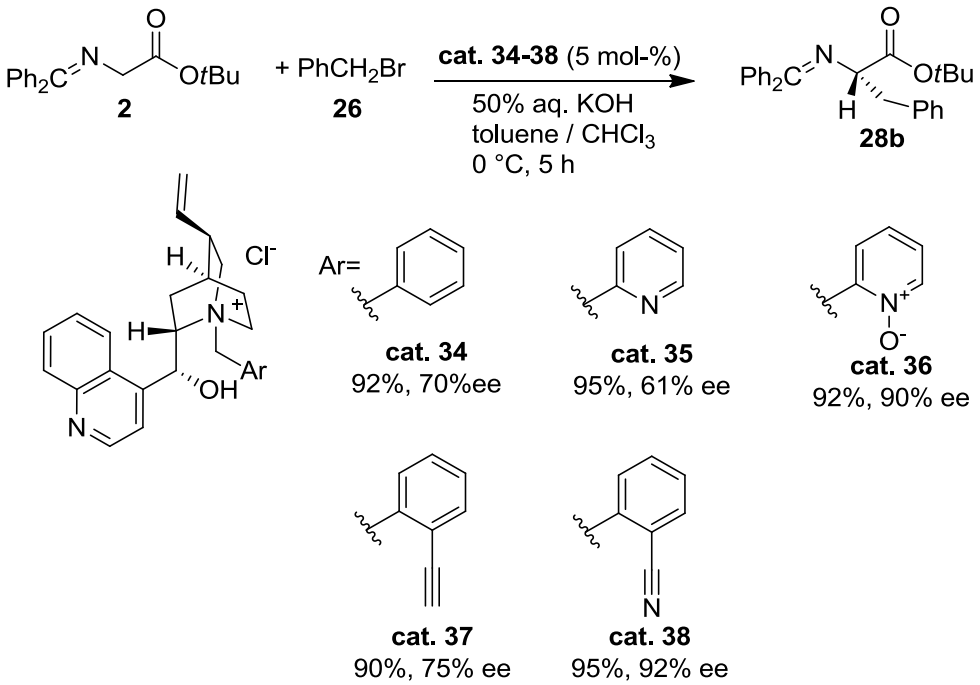
Jew, Park and co-workers also decided to study the electronic effect of aromatic fluorines on phase-transfer catalysts in 2002 (Scheme 7).



Scheme 7. The electronic effect of fluorine atoms on the enantioselectivity.

The group expected the electron-withdrawing functional groups to increase the enantioselectivity by the formation of a tighter binding ion pair, which would lead to a more rigid conformation. Unfortunately the results did not support this theory, at least not in the case of *meta*- or *para*-substitution. *Ortho* substitution did seem to marginally enhance the enantioselectivity. [19]

Jew and co-workers were encouraged by the results for the electron withdrawing effect caused by ortho-substituted catalysts and decided to further study the electronic effect by adding electron withdrawing groups solely at the *ortho*-position (Scheme 8).



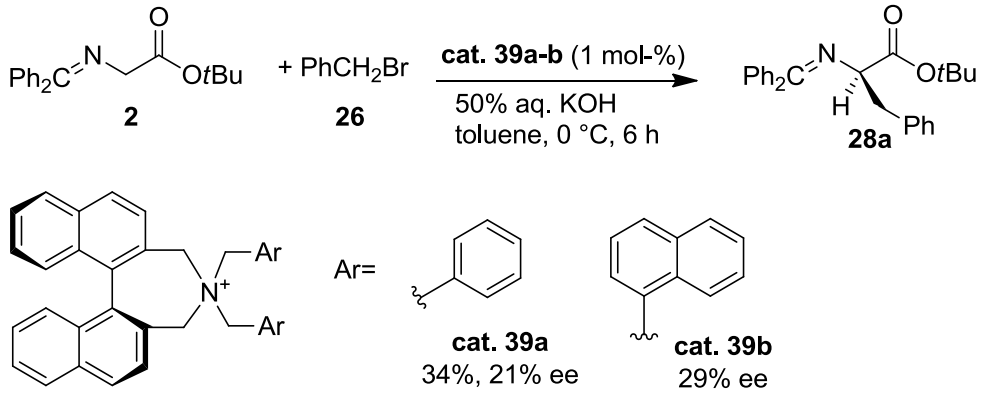
Scheme 8. Using electron withdrawing groups to enhance the enantioselectivity.

They proposed that the high enantioselectivity might be due to electronic interactions involving water between the oxygen at C(9) and an electronegative group such as 2'-CN in the catalyst. Hydrogen bonding or an induced dipole-dipole interaction, for example, would therefore give the catalyst a more rigid conformation. [20]

2.2. Non-*Cinchona* derived catalysts

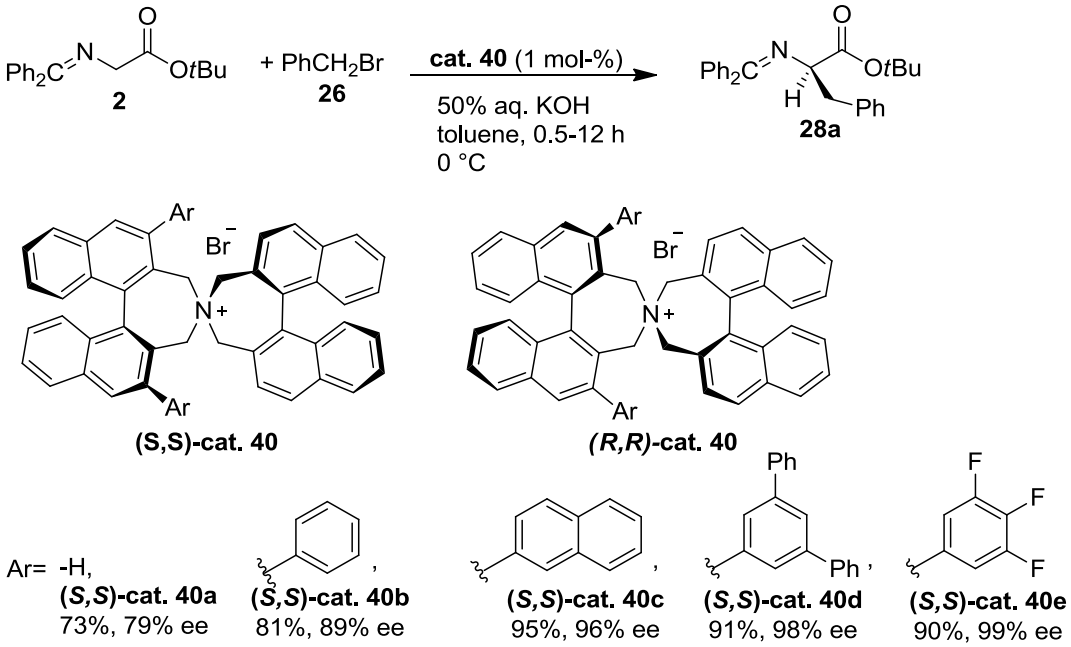
Chiral *spiro* ammonium salts

The next step in the development of phase-transfer catalysts was the creation of chiral spiroammonium salts, like the ones developed by Maruoka and co-workers in 1999. They sought a non-*Cinchona* alkaloid derivative that could be rationally designed and fine-tuned to suit their reactions. They initiated the search for such a catalyst by using commercially available (*S*)-binaphthol as the chiral unit of the spiroammonium salt (Scheme 9). [21]



Scheme 9. First generation of C_2-symmetric chiral quaternary ammonium salts created by Maruoka and co-workers.

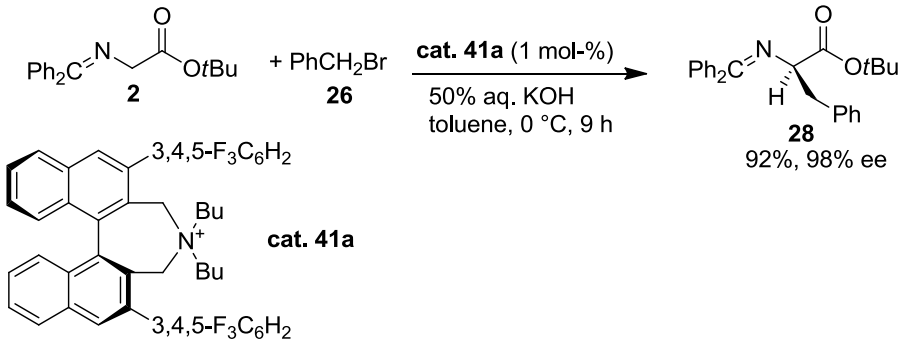
The results from the reaction above prompted the group to create a structurally more rigid chiral spiroammonium salt. By varying the aromatic substituent at the 3,3' position at one of the binaphthyl subunits of the catalyst, the enantiofacial discrimination could be varied. [21,22] The best results were achieved by varying the aromatic substituents, and are gathered below (Scheme 10).



Scheme 10. Second generation of C_2-symmetric chiral quaternary ammonium salts created by Maruoka and co-workers.

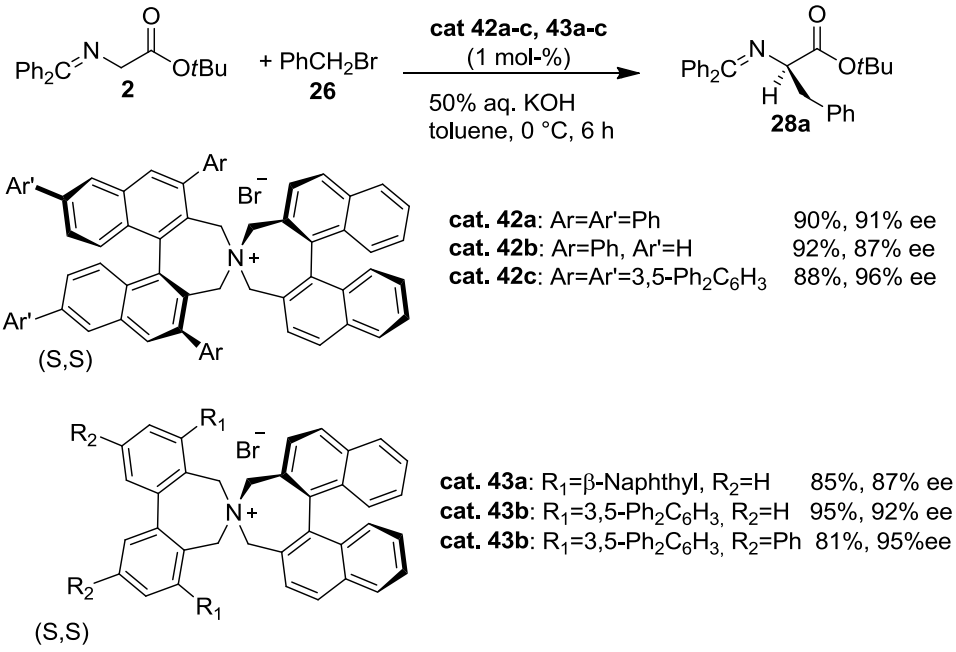
Maruoka and co-workers discovered in 2005 that by adding a fluoro-substituted phenyl ring to the binaphthyl unit and changing the aromatic ammonium substituents

for hydrocarbon chains, the enantioselectivity could be increased trifold compared to the first generation catalysts (Scheme 10) [23].



Scheme 11. Improved first generation Maruoka catalyst.

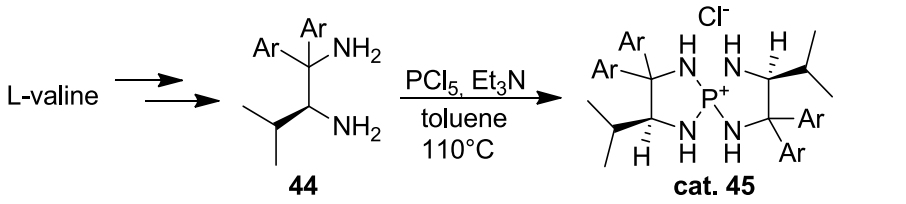
Maruoka further decided to improve the catalyst series by expanding the chiral environment and by varying the second unit in the catalyst. A few examples of these variations are presented below (Scheme 12). [24,25]



Scheme 12. Variations of the chiral quaternary ammonium salts created by Maruoka and co-workers.

Tetraaminophosphonium salts

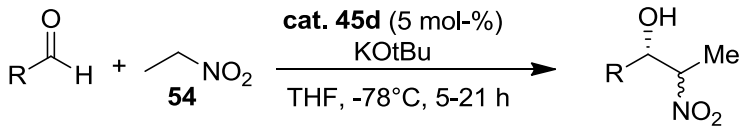
Ooi and co-workers decided to create their own catalyst series using chiral tetraaminophosphonium chloride for use in asymmetric phase-transfer. The structure of the chiral tetraaminophosphonium chloride (cat. **45**) from which the development began was readily synthesized from the parent α-amino acid, L-valine (Figure 4). [26]



45a Ar = Ph 92%
45b Ar = *m*-Xylyl 63%
45c Ar = *p*-Tolyl 94%
45d Ar = *p*-CF_3-C_6H_4 99%

Figure 4. Development of chiral tetraaminophosphonium chloride.

This catalyst was then used in the asymmetric direct Henry reaction of nitroalkanes to benzaldehydes (Scheme 13). [26]

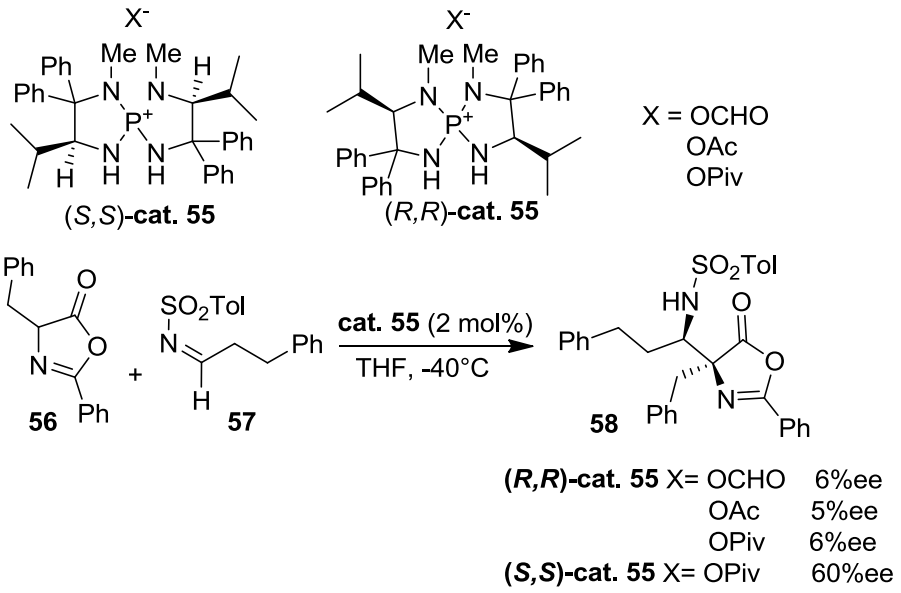


46 R = *o*-F-C_6H_4
47 R = *p*-F-C_6H_4
48 R = 2-furyl
49 R = (*E*)-PhCH=CH

50 R = *o*-F-C_6H_4 94%, 96% ee
51 R = *p*-F-C_6H_4 91%, 97% ee
52 R = 2-furyl 96%, 97% ee
53 R = (*E*)-PhCH=CH 74%, 99% ee

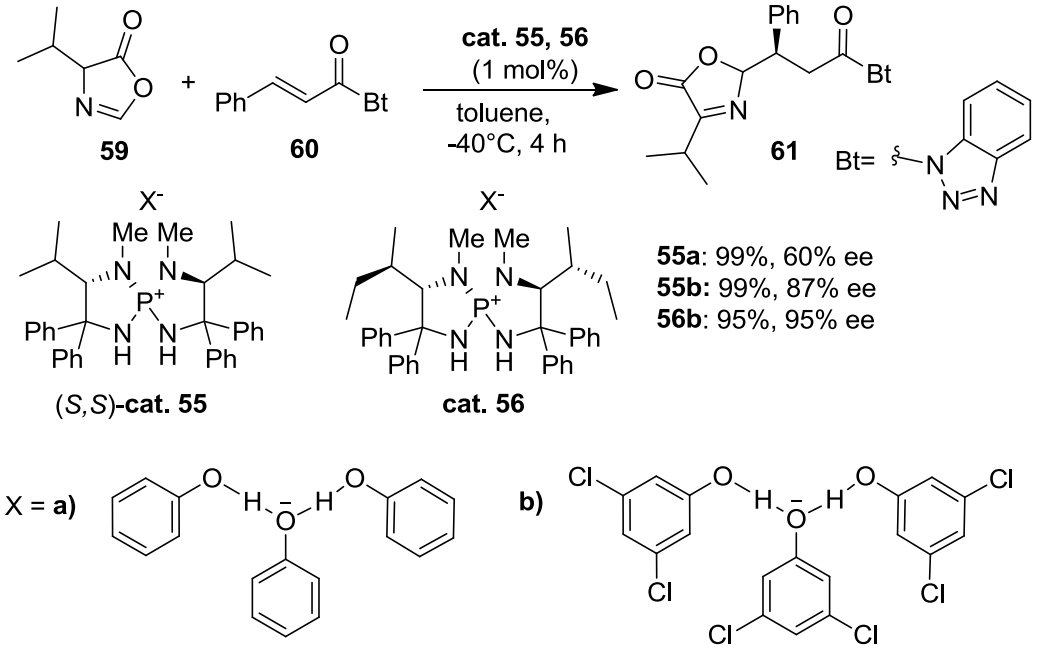
Scheme 13. Chiral tetraaminophosphonium salt mediated asymmetric Henry reaction of nitroalkanes to benzaldehydes.

The next step in the development of their chiral catalyst family was tuning the basicity of the anionic component. In 2008 it was attempted by using carboxylates as the anion part of the salt (Scheme 14). [27]



Scheme 14. Chiral tetraaminophosphonium carboxylate-catalyzed direct Mannich-type reaction.

The following year they decided to tune the anionic part of the salt in the following way (Scheme 15) [28]:



Scheme 15. Chiral tetraaminophosphonium phenoxide-catalyzed reaction.

The single-crystal X-ray diffraction analysis of the solid state structure of the salt with the anionic component **55**·$(OPh)_3H_2$ revealed that the aminophosphonium cation,

together with the two phenols and the phenoxide anion was aligned through a 10-membered cyclic network of intermolecular hydrogen-bonding interactions. Ooi hypothesized that the additional hydrogen bond from N-H protons in the phosphonium cation enhances the hydrogen bonding donor capability of the phenols, thus aiding the construction of an antidromic circular network. In addition, it is believed that the phenols effectively relay the stereochemical information in the chiral cation moiety, thus extending the chiral environment around the remotely located phenoxide anion. [28]

When the order of additions in the reaction was examined, the results indicated that the preorganization of the catalyst is not a prerequisite for the generation of the catalyst-substrate complex. These results implied that the selectivity could be tunable through structural modification of the achiral phenolic component. The role of a requisite molecular assembly was also supported when Ooi and co-workers succeeded in improving the enantioselectivity by increasing the catalyst loading and decreasing the solvent volume. [28]

In 2011, Ooi and co-workers used ^{31}P NMR spectroscopy to measure the structure of catalyst **55**·$(OPh)_3H_2$ in solution. In connection to the measurement, they found a phenomenon regarding the mode of molecular association. There seems to be three possible molecular assemblies in solution, which can easily be adjusted by adjusting the stoichiometry of the anionic component of catalyst **55**·$(OPh)_nH_{(n-1)}$ (Figure 5). [29]

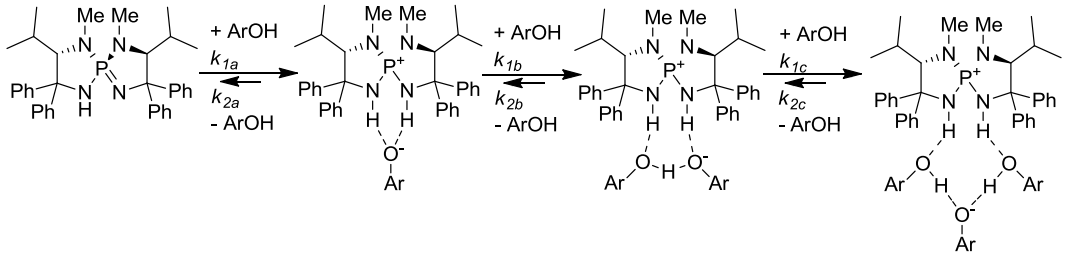
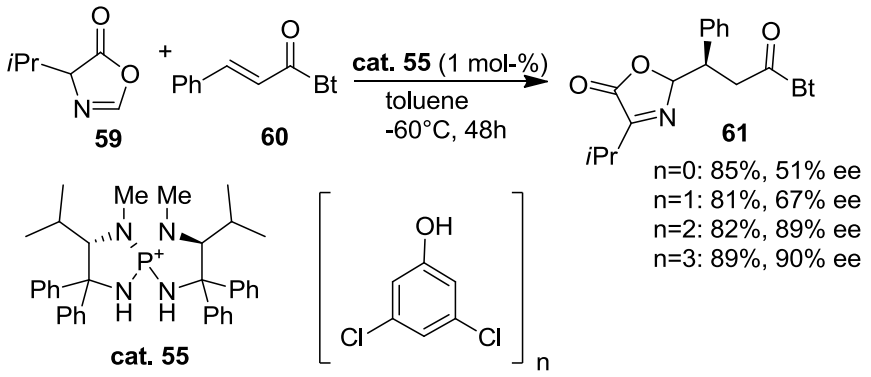


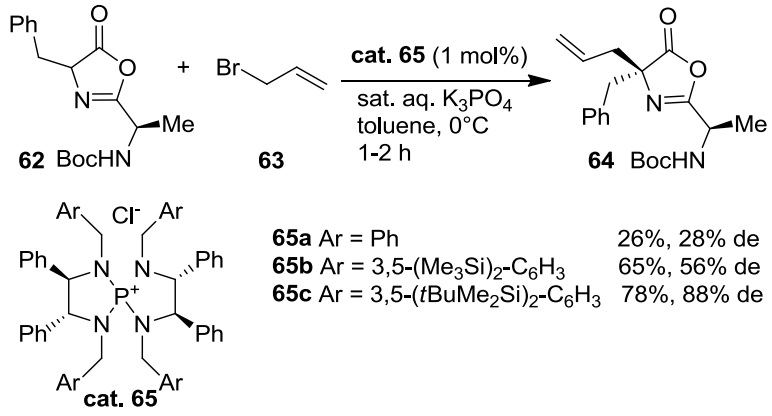
Figure 5. Equilibrium between molecular assemblies.

Each of the above mentioned assembly has been confirmed by x-ray crystallographic analysis of the solid state. It seems that n=3 is the maximum amount in the molecular association. The number of anionic components incorporated in the catalyst assembly affects the enantioselectivity, however, the increase of the enantioselectivity between n = 2 and n = 3 is minimal (Scheme 16). [29]



Scheme 16. Asymmetric conjugate addition catalyzed by chiral tetraamino-phosphonium aryloxide assemblies.

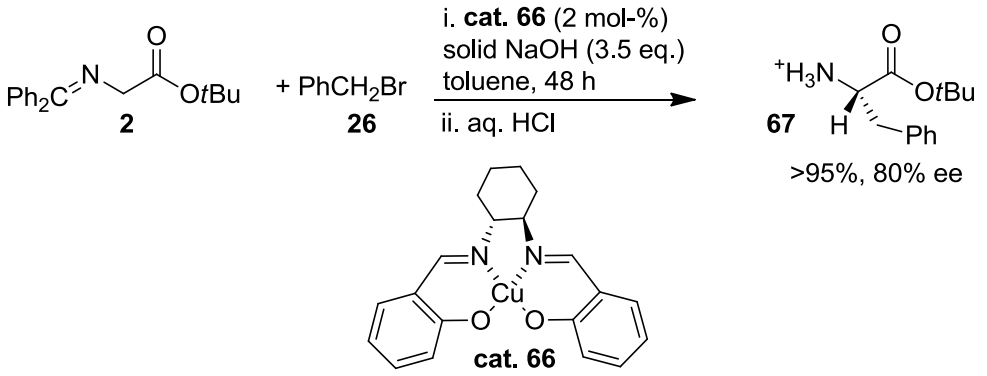
In 2009, the group created another chiral tetraaminophosphonium salt, prepared this time from the commercially available (*R,R*)-1,2-diphenylethylenediamide In the study they aimed at developing a method for the incorporation of a variety of chiral, nonracemic, quaternary α-amino acids as specific sites of a peptide strand using their new catalyst (Scheme 17). [30]



Scheme 17. Chiral tetraaminophosphonium chloride catalyzed alkylation of an azlactone.

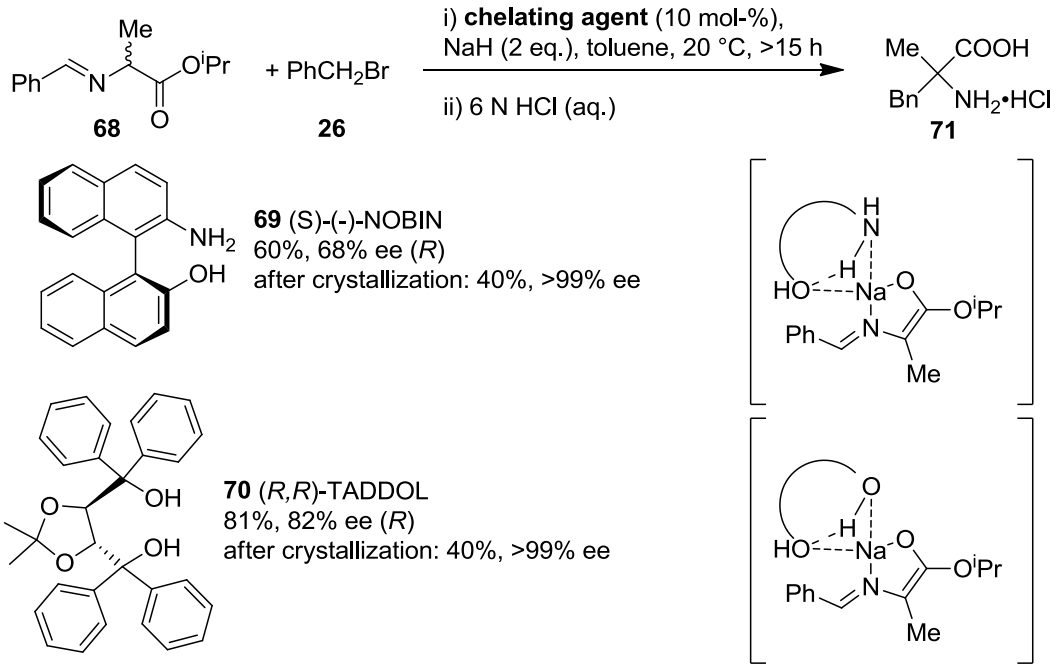
Other chiral catalysts

Other interesting catalysts are for example the chiral copper-salen complex **66** reported by Belokon and co-workers (Scheme 18) [31].



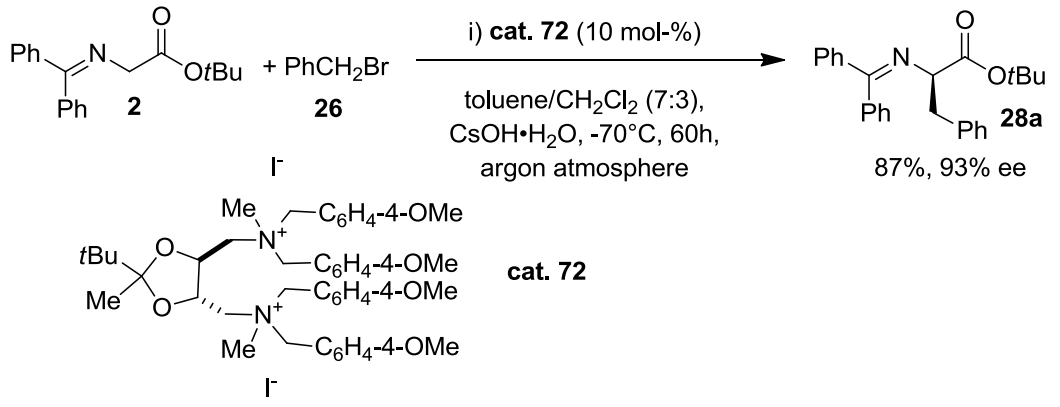
Scheme 18. Copper-salen complex catalyzed alkylation reported by Belokon and co-workers.

Their idea for this catalyst came from their studies utilizing TADDOL (α,α,α,α-tetraaryl-1,3-dioxolane-4,5- dimethanols) and NOBIN (2-amino-2'-hydroxy-1,1'-binaphthyl) as the chelating agent for the alkali ions, making the ion-pair of the corresponding carbanion and alkali ion soluble in organic solvents (Scheme 19). They then decided to combine the synthetic simplicity of the phase-transfer catalysis with the advantages of catalysis by metal complexes in their study of the chiral copper-salen complex **66**. [32, 33]



Scheme 19. TADDOL and NOBIN catalyzed phase-transfer catalysis.

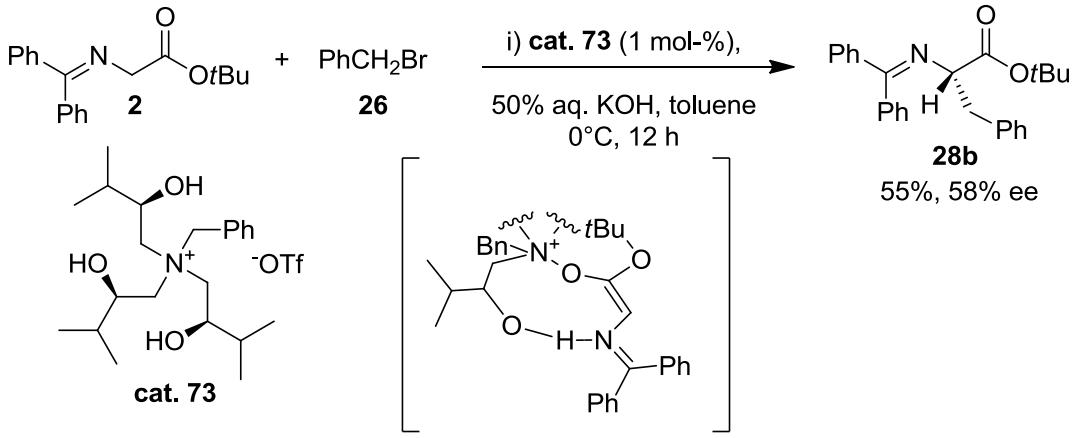
Shibasaki and co-workers approached the creation of their own catalyst by first performing a molecular mechanics simulation using the Monte Carlo method. The results suggested that the Schiff base of *tert*-butyl glycinate would place itself between both ammonium cations of the catalyst in the way the group had hoped. They then proceeded with synthesizing a variety of catalysts from L- and D-tartrate, varying the ketal moieties and the aromatic parts (Scheme 20). [34]



Scheme 20. Asymmetric phase-transfer alkylation utilizing the two-center tartrate catalyst by Shibasaki and co-workers.

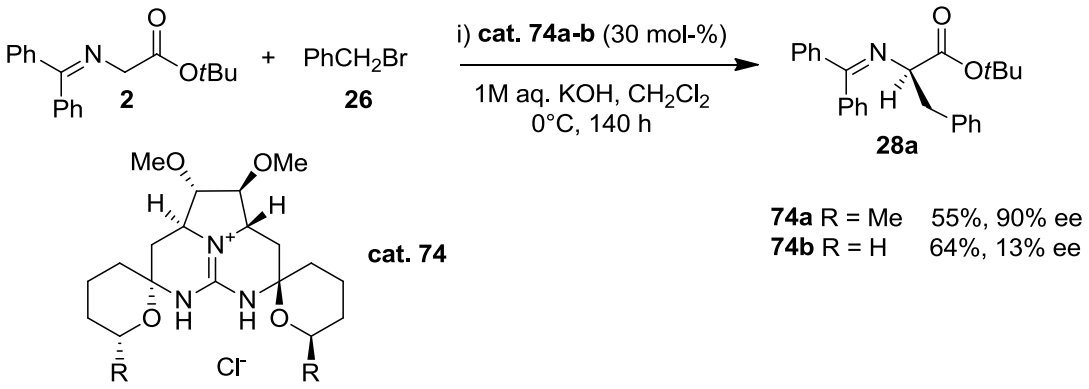
Takabe and co-workers also attempted to create their own catalyst series. They prepared the C_3-symmetric amine-based chiral phase-transfer catalyst **73** presented

below (Scheme 21). Takabe and co-workers attributed the enantioselectivity to the hydrogen bonding between one of the chiral hydroxyl groups and the nitrogen in the Schiff base. [35] However, neither the yield nor the enantioselectivity was especially good, which might be attributed to the flexibleness of the catalyst.



Scheme 21. Asymmetric phase-transfer alkylation utilizing a C_3-symmetric amine based chiral phase-transfer catalyst.

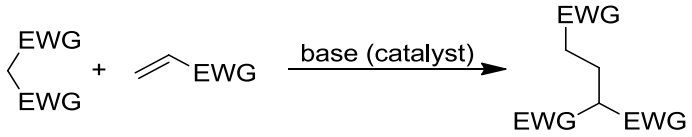
Nagasawa and co-workers used a C_2-symmetric chiral cyclic guanidine catalyst **74** in their asymmetric alkylation of a Schiff base (Scheme 22). They found that the methyl substituent was crucial for enantiomeric enhancement.



Scheme 22. Asymmetric phase-transfer alkylation utilizing a C_2-symmetric chiral cyclic guanidine catalyst.

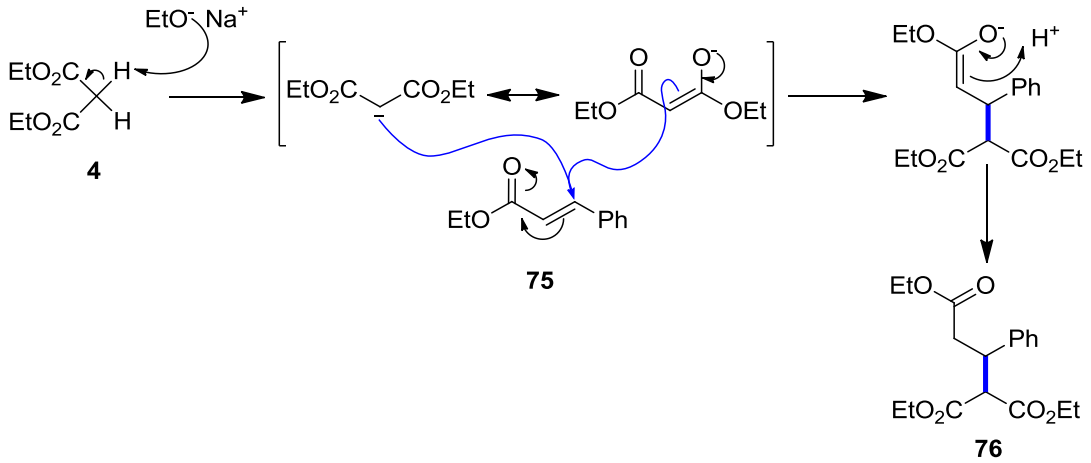
3. Michael addition

Conjugate addition is synthetically a most versatile bond forming strategy (Scheme 23). This is mainly due to the broad spectrum of donors (nucleophiles) and acceptors (alkenes and alkynes attached to an electron withdrawing group (EWG)). The nucleophile can be carbon or heteroatom based, and the diversity in acceptors arises from the broad variety of activating EWG groups (ketones, aldehydes, esters, amide, nitriles, nitro, sulfones, sulfoxides, phosphates etc.)



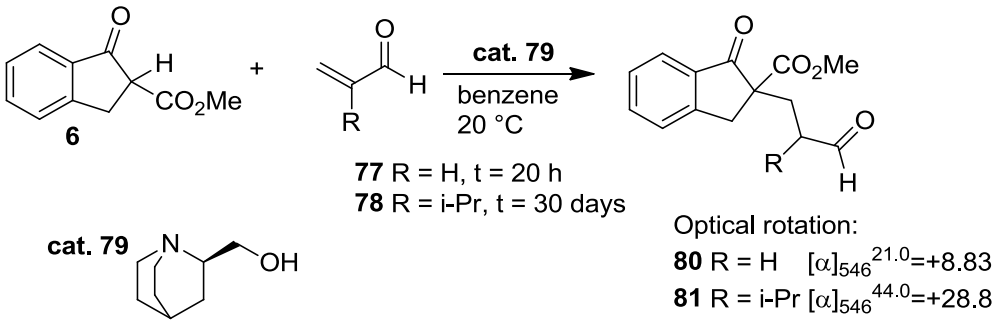
Scheme 23. The 1,4-addition of resonance stabilized carbanions.

In the late nineteenth century (1887) Arthur Michael found that the enolate anion derived from diethyl malonate reacts with ethyl cinnamate at the β-carbon to give the enolate anion as the product (Scheme 24) [36]. The two stage mechanism (addition followed by protonation) is preceded by first deprotonating the nucleophile by a base to form a resonance stabilized carbanion that can react with the ethyl cinnamate.



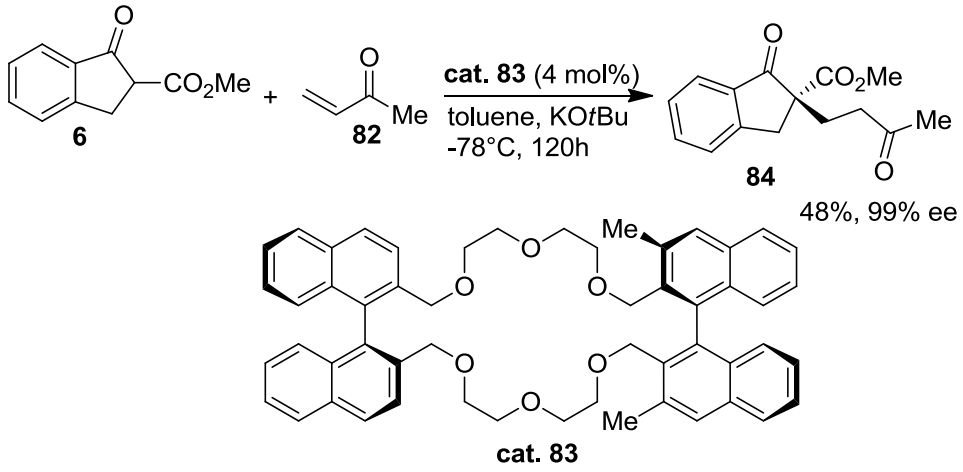
Scheme 24. The reaction of Arthur Michael.

Since then, many strategies for controlling the stereochemistry of the product have been developed. The first reported Michael type reaction utilizing a chiral catalyst was reported by Göran Bergson and Bengt Långström in 1973 (Scheme 25). [37]



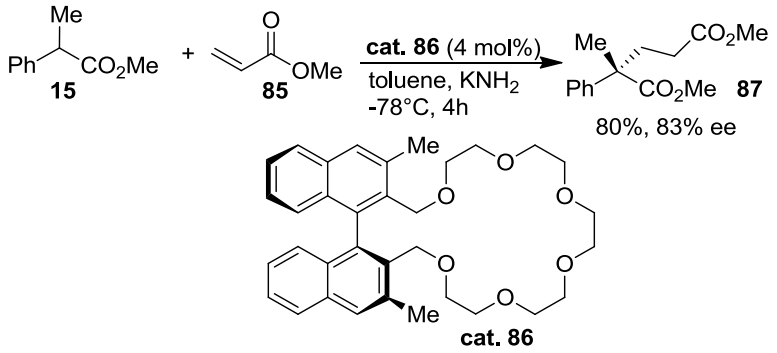
Scheme 25. First chiral catalyzed Michael-type reaction.

Michael addition has also been utilized in phase-transfer catalysis. The first successful Michael addition under phase-transfer conditions was accomplished by Cram and Sogah in 1981. Inspired by the results obtained by Bergson and Långström, Cram and Sogah decided to perform a similar reaction, but under phase-transfer conditions, with chiral crown ether **83** as the catalyst (Scheme 26). [3]



Scheme 26. First successful enantioselective Michael addition under phase-transfer condition.

Another successful enantioselective Michael addition accomplished in the same study utilized a smaller chiral crown ether in the reaction of methyl 2-phenylproprionate **15** with methyl acrylate **85** (Scheme 27). [3]



Scheme 27. Chiral crown ether catalyzed Michael addition.

In 1989 Kenji Koga and co-workers were inspired by Cram's results and decided to investigate chiral crown ethers. By varying the position, length and electronic effect of the chirality administering group, they hoped to acquire more information about the chiral recognition (Figure 6). [38]

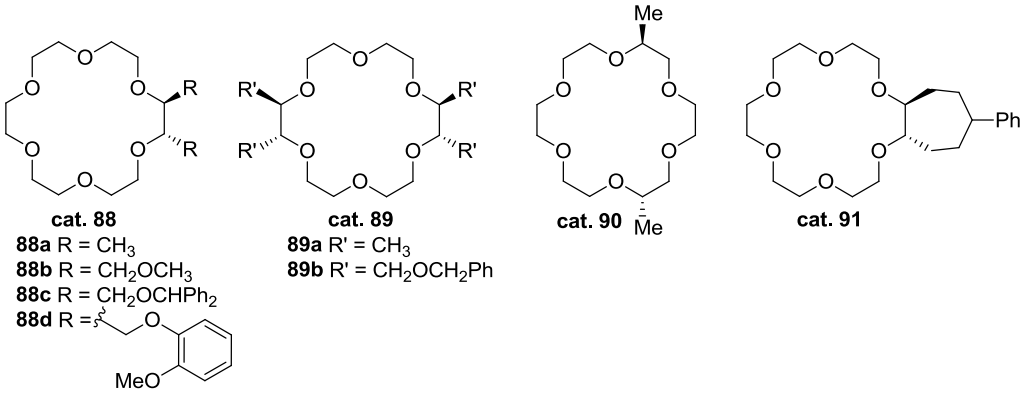
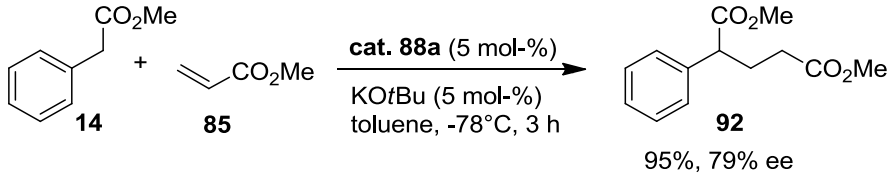


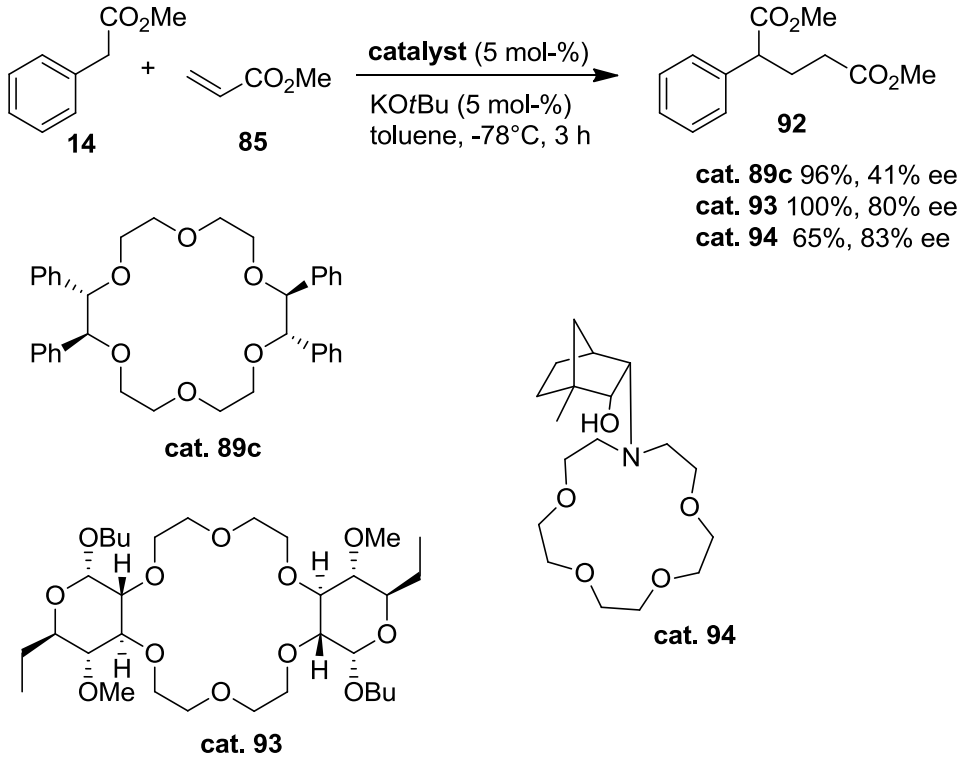
Figure 6. The chiral catalysts of Koga and co-workers.

Crystal structures of catalysts **88** and **89** indicate that the potassium cations are located in the center of the crown structure and that the vicinal methyl groups are anti to each other and diaxial-like. The results from the study suggested that to be effective the methyl groups must be vicinal and diaxial-like in the crown potassium enolate complex. The best results were obtained with catalyst **88a** (Scheme 30). [38]



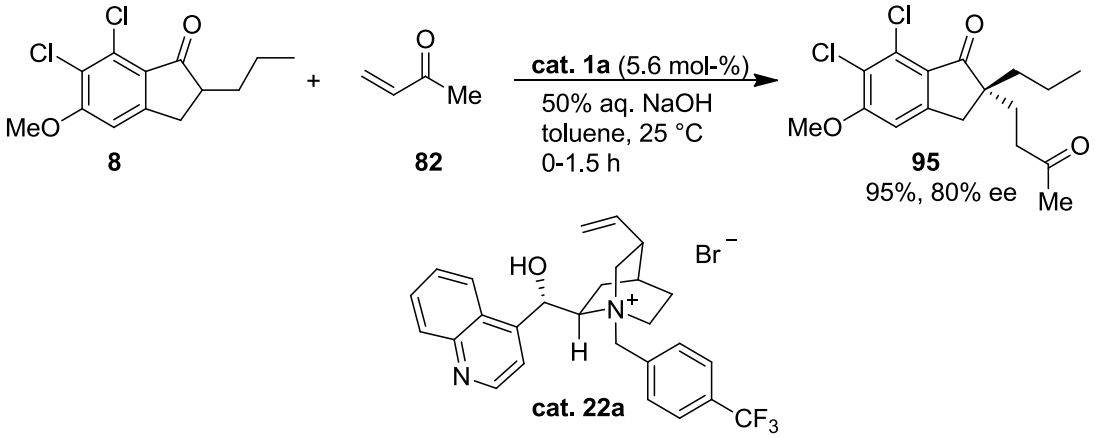
Scheme 28. Best results acquired by Koga and co-workers.

Other chiral crown ethers used for this type of reaction are catalysts **89c**, **93** and **94** (Scheme 29). [2]



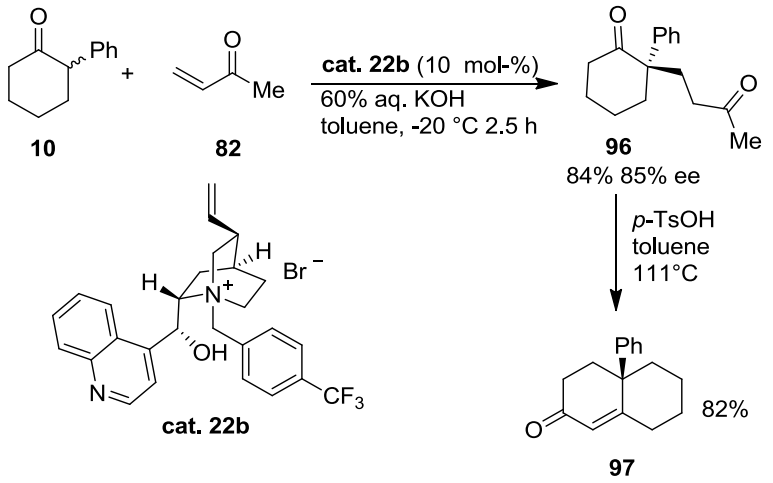
Scheme 29. Other crown ethers that have been applied in phase-transfer catalysis.

In 1986, Conn and co-workers, a research group at Merck decided to stereoselectively functionalize 2-alkylindanones using their original catalyst **22a** (Scheme 30). [39]



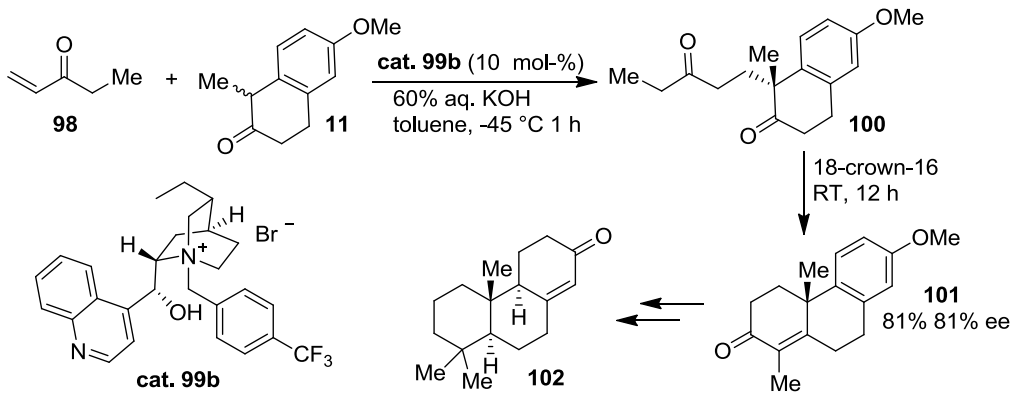
Scheme 30. Michael addition of Conn and co-workers.

Cinchona alkaloid derived catalysts have further been applied in this field. For example Vandewalle and co-workers decided in 1990 that they wanted to do extensive research on the subject of asymmetric alkylation of α-aryl substituted carbonyl compounds by means of chiral phase-transfer catalysts. With a few target molecules in mind they chose 3 tetralones, 2 non-fused α-arylketones, a lactone and an acyclic ketone for their study on asymmetric alkylation of α-aryl substituted carbonyl compounds. The best result in the category of non-fused substrates is shown in Scheme 31. [40]



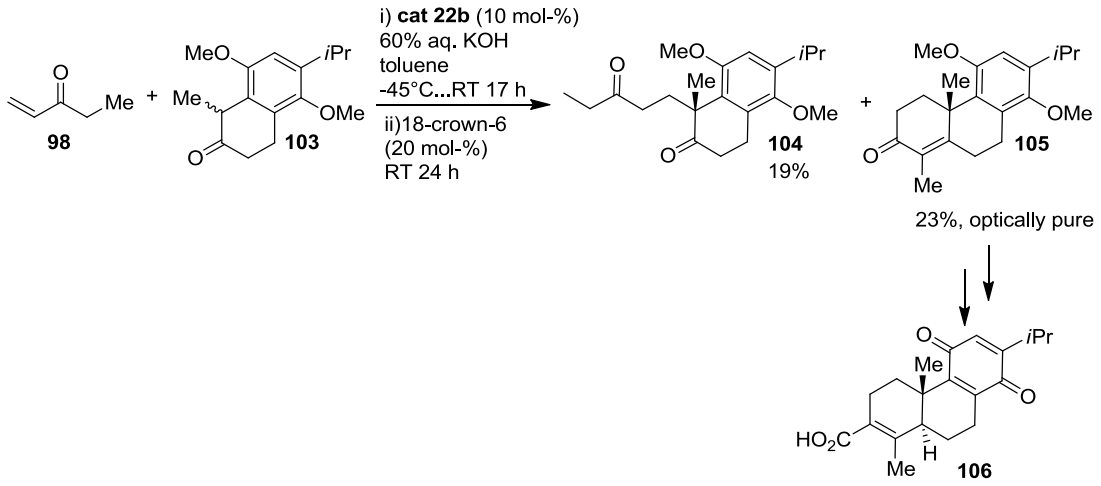
Scheme 31. Robinson annulation of 2-phenylcyclohexanone with methyl vinyl ketone.

Encouraged by the results they decided to attempt the total synthesis of (+)-podocarp-8(14)-en-13-one. One of the steps contained the asymmetric Michael addition of a tetralone derivative to an enone, followed by a one-pot Robinson annulation (Scheme 32). [40]



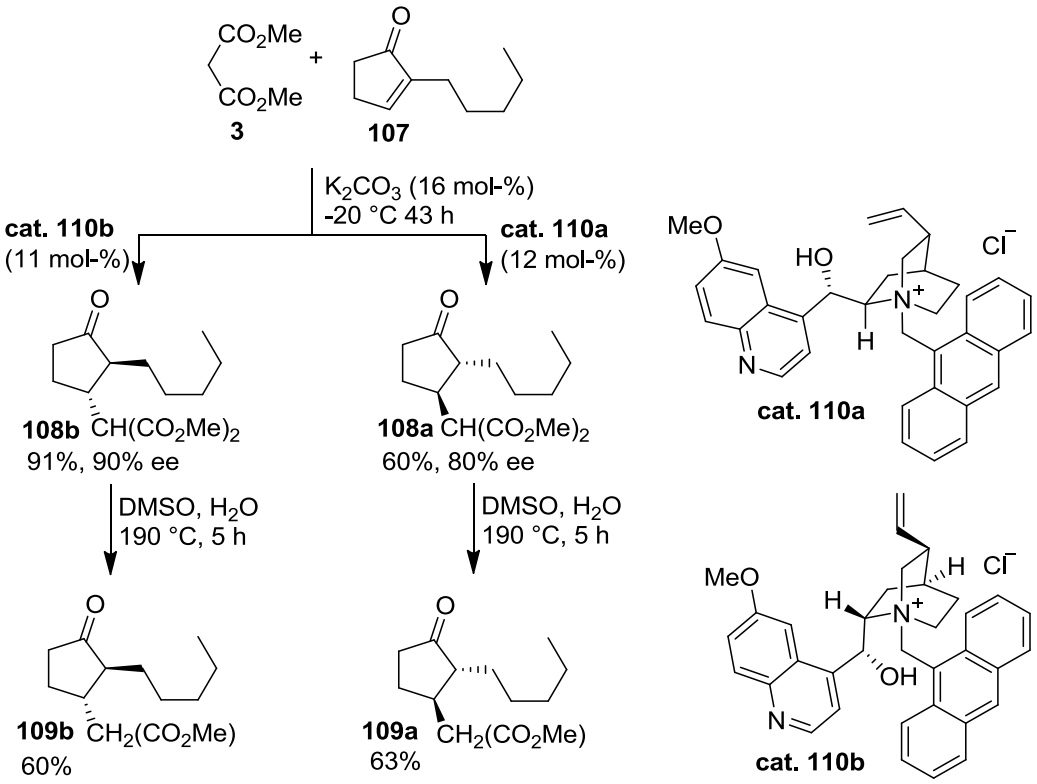
Scheme 32. Total synthesis of (+)-podocarp-8(14)-en-13-one.

In 1994 Shishido and co-workers were able to use the same route in their total synthesis of (+)-triptoquinone (Scheme 33). The only difference being that they used *N*-(*p*-trifluoromethyl)benzylcinchonidinium bromide **22b** as their chiral catalyst instead of the *N*-(*p*-trifluoromethyl)benzyldehydrocinchonidinium bromide **99b** used in the Vandewalle route.[41]



Scheme 33. Total synthesis of (+)-triptoquinone.

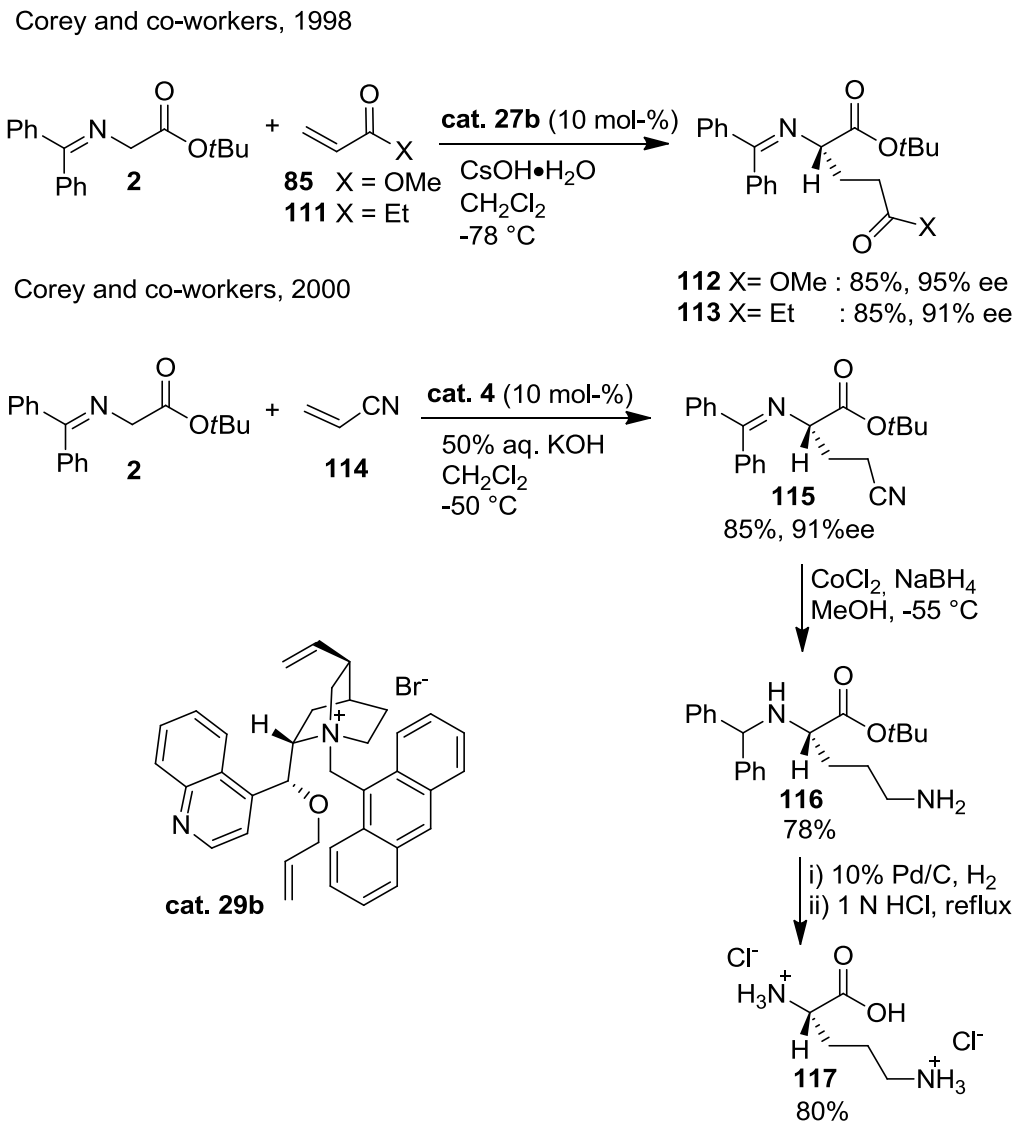
By utilizing *N*-(methylanthracenyl)quinidinium and -quininium chloride and solvent free conditions Plaquevent and co-workers hoped to be able to synthesize (-)-methyl dihydrojasmonate. This route enabled a short enantioselective synthesis of both enantiomers of methyl dihydrojasmonate (Scheme 34). [42]



Scheme 34. The solvent free Michael addition of Plaquevent and co-workers.

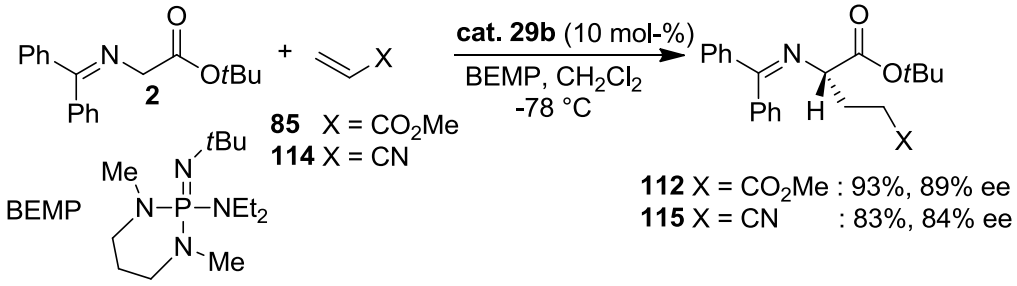
It is noteworthy that in most reports catalysts based on cinchonine usually give a lower enantioselectivity than catalysts based on cinchonidine.

Various functionalized α-alkyl amino acids have also been synthesized by enantioselective Michael addition of glycine derivatives. In 1998 Corey and co-workers added a glycinate Schiff base to α,β-unsaturated carbonyl substrates. In 2000 they used acrylonitrile as an acceptor, thus enabling the synthesis of (*S*)-ornithine as its dihydrochloride (Scheme 35). [11,43]



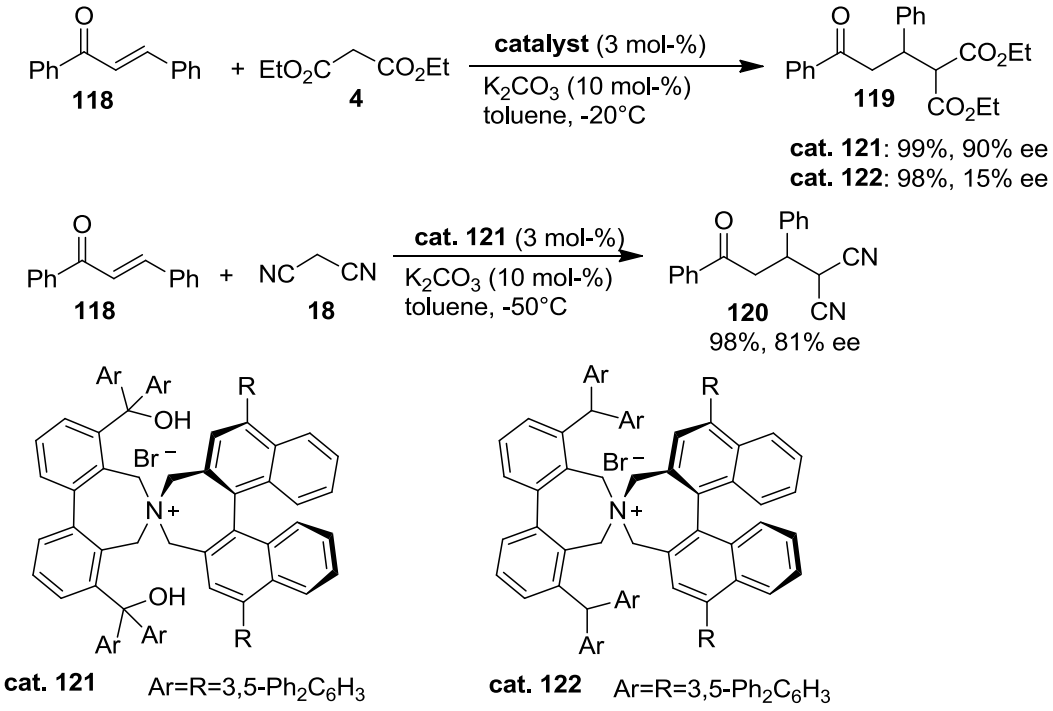
Scheme 35. Enantioselective Michael addition of glycine derivatives.

O'Donnell and co-workers substituted the base in the reaction above against organic-soluble, non-ionic bases BEMP and BTPP in 2001. In general, the less basic BEMP provided better results and tolerated several representative Michael acceptors. The group had been working on unnatural peptide synthesis since 1995, utilizing resin-bound Schiff base esters for the solid phase synthesis of unnatural amino acids and peptides. Their method utilizing BEMP and BTPP was also applied to the solid-phase peptide synthesis (Scheme 36). [44]



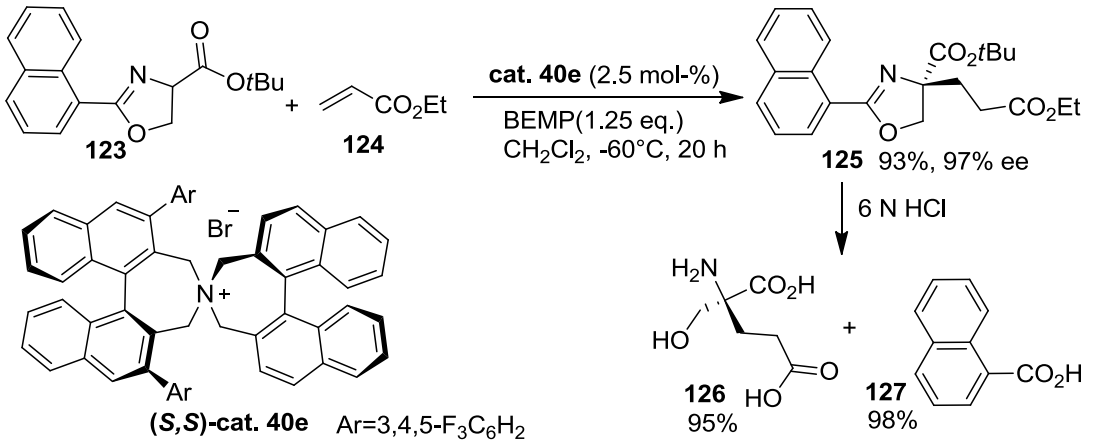
Scheme 36. Organo-soluble BEMP as base in Michael addition.

The chiral spiroammonium salts of Maruoka mentioned in Chapter 2 have also been used in asymmetric Michael additions. In 2005 Maruoka and co-workers decided to evaluate their spiroammonium salts in the Michael addition reactions of diethyl malonate and various chalcone derivatives. They also substituted the ester substituents of the malonate to study the steric effect on the enantioselectivity. By varying the electron donating/ withdrawing groups they were able to study the effect on the enantioselectivity. Lastly they exchanged the dialkyl malonates against malononitrile (Scheme 37). [45]



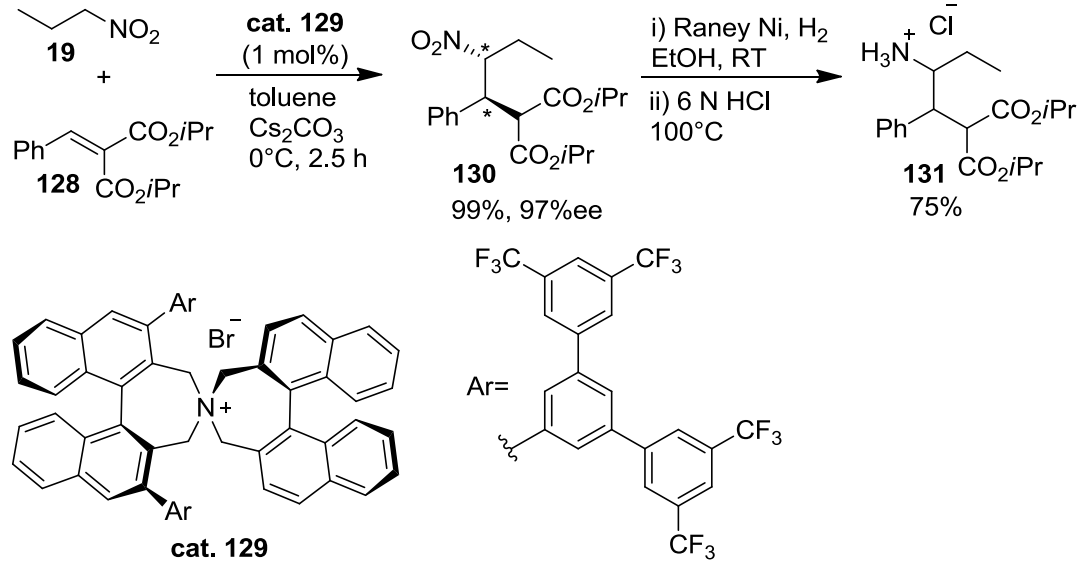
Scheme 37. Chiral spiroammonium salt catalyzed Michael reaction of chalcones.

Maruoka and co-workers' original spiroammonium salt was utilized in the total synthesis of (2*S*)-α-(hydroxymethyl) glutamate acid by Jew, Park and co-workers (Scheme 38). [46]



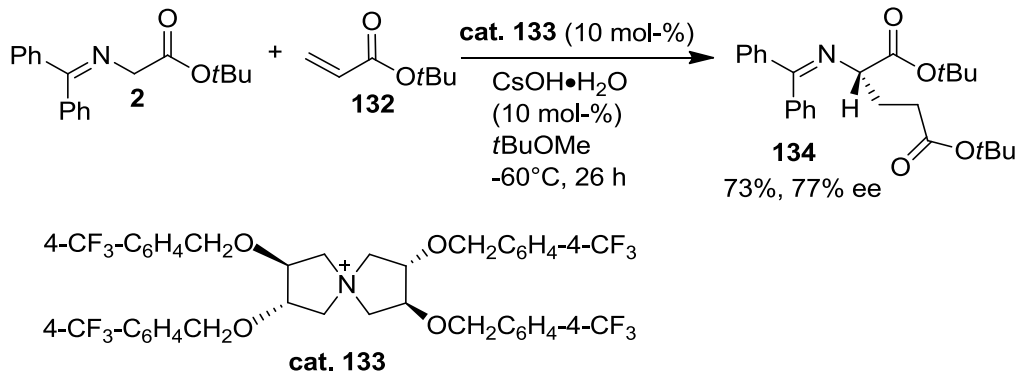
Scheme 38. Total synthesis of (2*S*)-α-(hydroxymethyl) glutamate acid.

Maruoka and co-workers wanted to create a method that would provide access to a variety of optically active γ-amino acid derivatives. Using their *N-spiro* C_2-symmetric chiral quaternary ammonium bromide catalyst they succeeded in the conjugate addition of nitro alkanes to alkylidenemalonates (Scheme 39). [47]



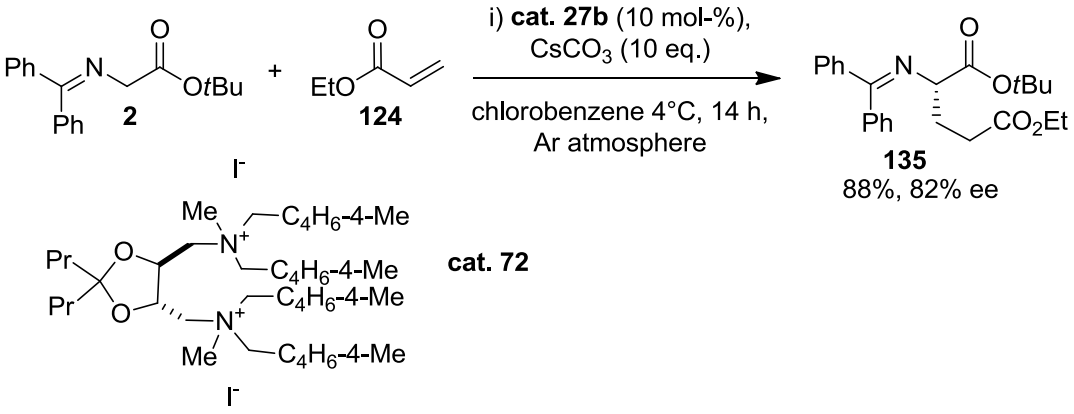
Scheme 39. Michael addition of nitropropane to an alkylidenemalonate.

Other interesting phase-transfer catalysts used in asymmetric Michael additions are for example Arai, Tsuji, and Nishida's tartrate derived *spiro* compound (Scheme 40) [48].



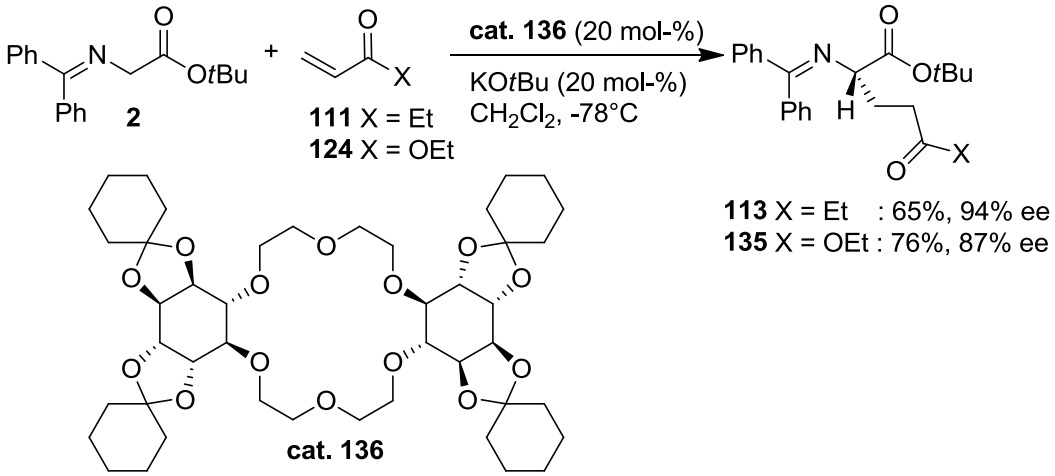
Scheme 40. Tartrate-derived *N*-spiroammonium salt catalyzed Michael addition.

The two-center tartrate catalyst developed by Shibasaki and co-workers mentioned in chapter 2.2 was also utilized in a Michael addition (Scheme 41). [34]



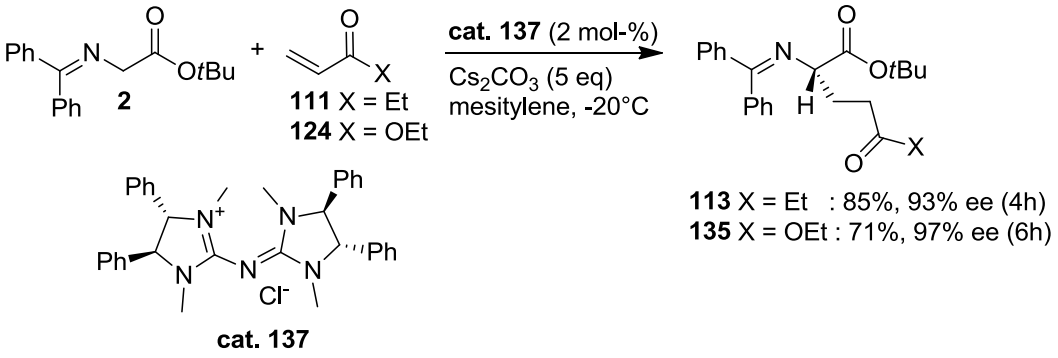
Scheme 41. Two-center tartrate catalyzed Michael addition.

In 2003 Akiyama and co-workers decided to renew the "traditional" crown ether starting the catalyst synthesis from L-quebrachitol, an optically active *chiro*-inositol obtained from the exudate of rubber trees (Scheme 42) [49].



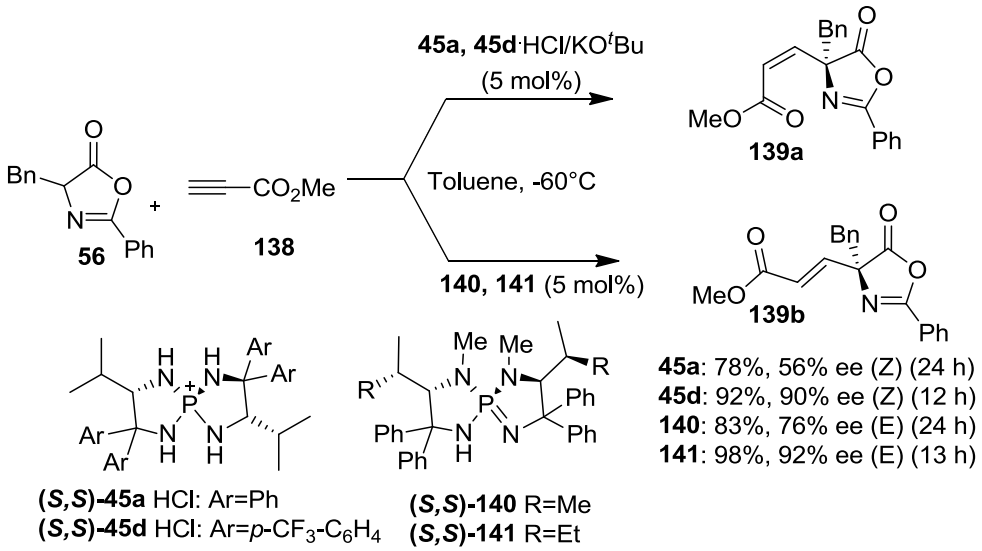
Scheme 42. *Chiro*-inositol-derived crown ether catalyzed Michael addition.

As a continuation on their work with bicyclic guanidines as chiral Brønsted base catalysts, Tan and co-workers decided to try and create structures more basic than guanidines. Pentanidine, a structure with five nitrogen atoms in conjugation was hypothesized to be more basic. The alkylated salt proved to work as a phase-transfer catalyst. Scheme 43 shows an example of the results comparable to the previous examples in this literary review. [50]



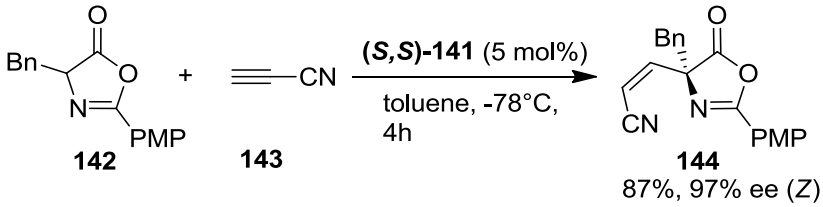
Scheme 43. Pentanidium chloride catalyzed Michael addition.

In 2013, Ooi and co-workers also decided to attempt an asymmetric Michael addition of electron-deficient triple bonds to azlactones with the help of closely related *p-spiro* chiral iminophosphorane catalysts mentioned in Chapter 2 (Scheme 44). [51]



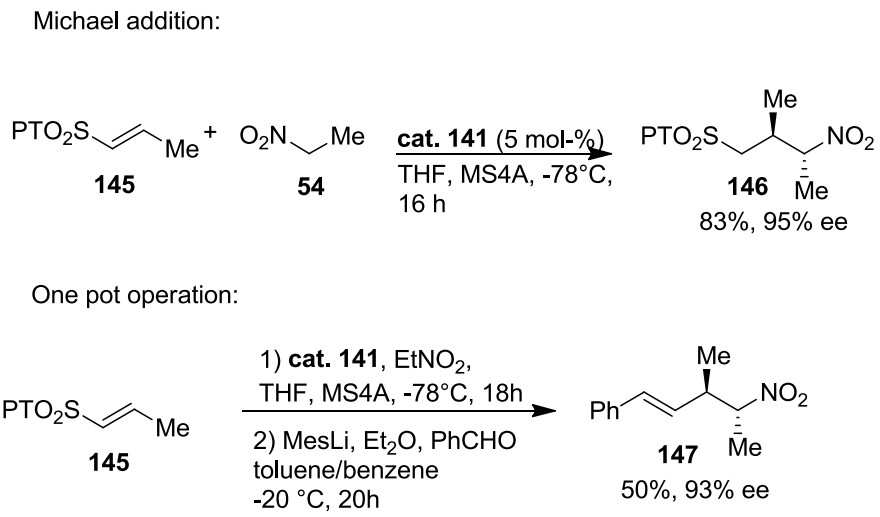
Scheme 44. Michael addition of electron-deficient triple bonds to azlactones.

Catalytic asymmetric Michael addition to electron-deficient triple bonds such as ynals, ynones and ynoates can be very challenging since they require geometric control of the newly formed olefin. The Ooi group proposed that the difference in the protonation pathway which is dependent on the proton donors, the conjugate acids of the catalysts as well as the properties of the electrophile, causes a complete switch of *E/Z*-selectivity. Their results indicated that protonation followed the *O*-protonation pathway rather than the common *C*-protonation pathway. In order to confirm this, they employed cyanoacetylene as a new Michael acceptor (Scheme 45). Due to the carbanionic character of the intermediate α-cyano vinylic anion generated through the addition of a nucleophile, the contribution of the *N*-protonation pathway is expected to be negligible. Thus the direction of the proton transfer to the anionic carbon should be directly reflected in the *E*/*Z*-selectivity of the Michael adduct. [51]



Scheme 45. Michael addition of an electron-deficient triple bond to a cyanoacetylene.

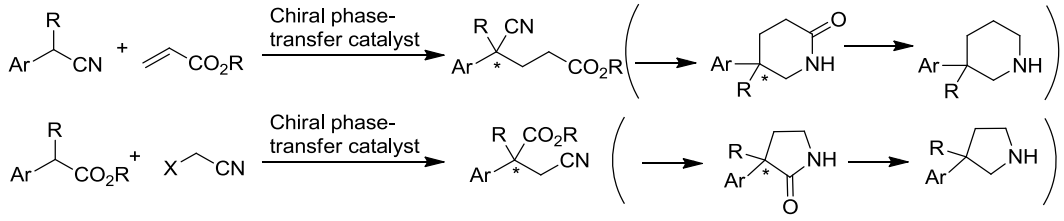
Ooi and co-workers continued their work with catalyst **141**, using it for the enantioselective formal α-allylation of nitroalkanes through a catalyzed Michael reaction-Julia-Kocienski olefination sequence (Scheme 46). [52]



Scheme 46. One-pot operation of chiral iminophosphorane catalyzed Michael reaction-Julia-Kocienski olefination sequence (PT = 1-phenyl-1*H*-tetrazol-5-yl).

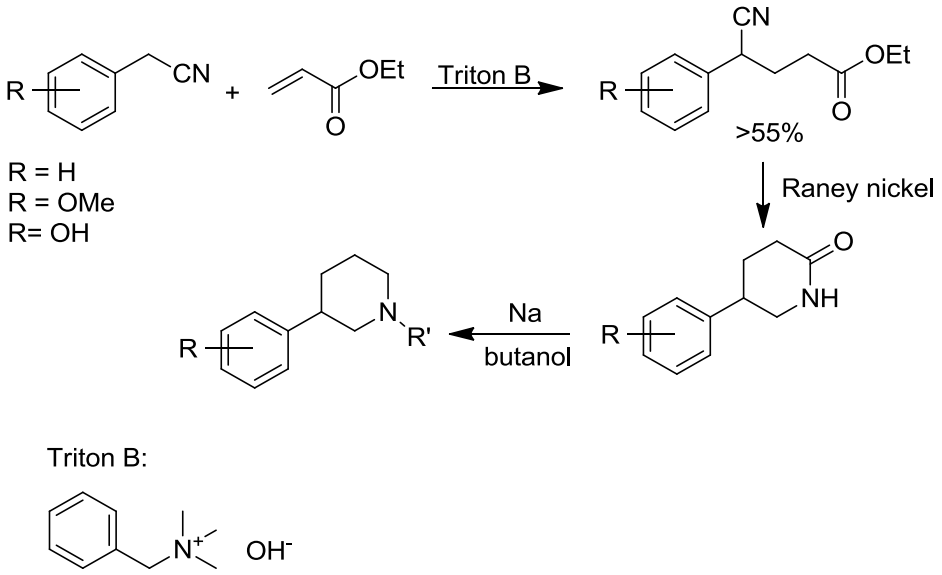
4. Results and discussion

The aim of this study was to develop a method by which new stereocenters could be generated via chiral phase-transfer catalysis. The compounds could then be transformed for example to heterocycles (Scheme 47).



Scheme 47. The aim of the thesis.

M. Julia and co-workers utilized this route, including the Michael addition, to synthesize a number of racemic 3-aryl-piperidines in 1968 (Scheme 48). [53]



Scheme 48. Julia and co-workers' route to 3-aryl-piperidines.

They thus created for instance the following 3-aryl-piperidines (Figure 8).

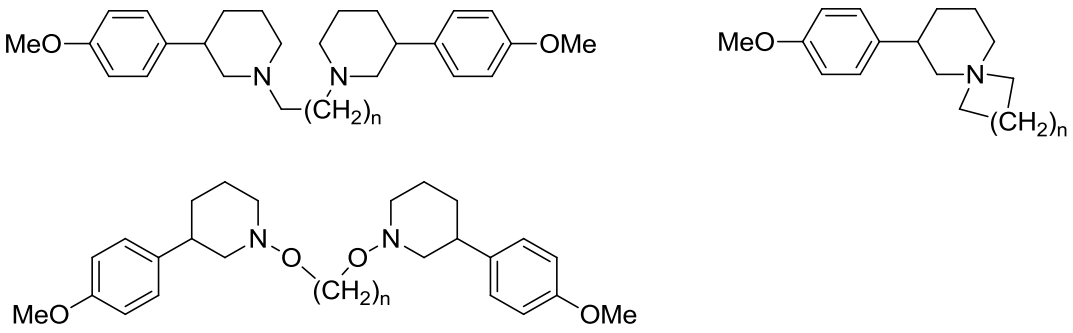
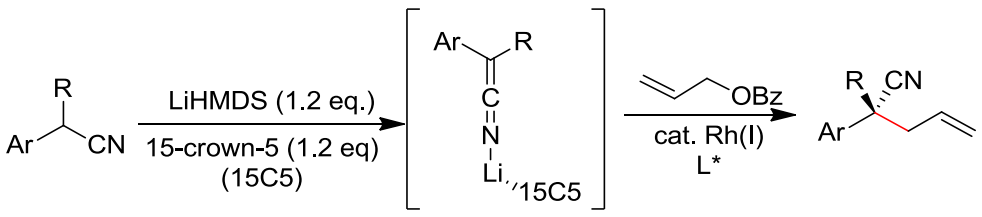


Figure 7. Racemic 3-aryl piperidines of Julia and co-workers.

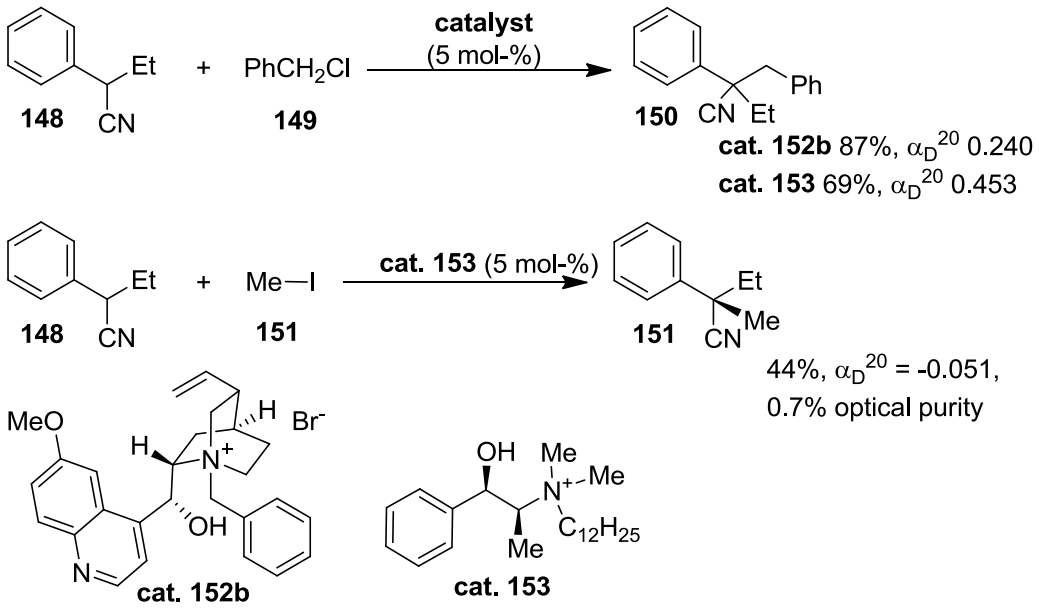
Evans and Turnbull published an article in May this year with a similar process in mind as M. Julia and co-workers, only utilizing another mechanism (Scheme 49). [54]



Scheme 49. Rhodium-catalyzed allylic substitution with a nitrile anion.

The first chiral phase-transfer catalyzed alkylation utilizing a similar starting material was first executed in 1980 by S. Juliá and co-workers. They used a chiral quaternary

ammonium salt derived from ephedrine and a quinidinium salt to provide the enantioselectivity for the reaction (Scheme 50). With the ephedrine salt **153** they succeeded in obtaining an enantioselectivity of 0.7%. [55]



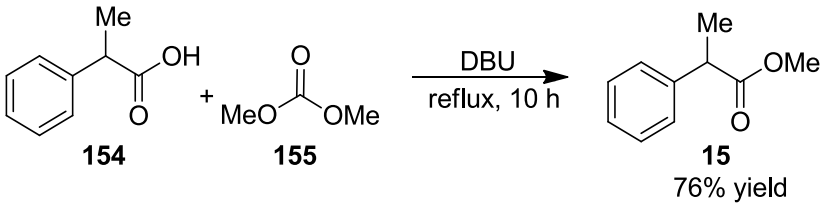
Scheme 50. The first chirally catalyzed alkylation of α-ethylbenzyl cyanide.

4.1. Starting point

Expecting the route of Julia and co-workers to be possible to execute in an enantioselective manner by using a phase-transfer catalyst commercially available or synthesizable from literature, three main catalyst categories were chosen for further evaluation. The first category was the well-studied and much utilized *Cinchona* alkaloid, the second category was the chiral tetraminophosphonium salts created by Ooi and co-workers and the last category was the pentanidium salts created by Tan and co-workers. The C_2-symmetric chiral quaternary ammonium salts of Maruoka and co-workers aroused interest, but unfortunately the synthesis of the catalysts developed by Maruoka and co-workers were far too laborious and time consuming for this thesis.

Previous unpublished results from this laboratory indicated that ethyl phenylacetate was prone to double addition, so a decision was made to begin the optimization of the reaction with an α-substituted reactant. Hoping that methyl 2-phenylpropanoate **15** used in the chiral phase-transfer catalysis by Cram and Sogah (Scheme 27) would give a little more steric bulk than an α-methylbenzyl cyanide it was synthesized from

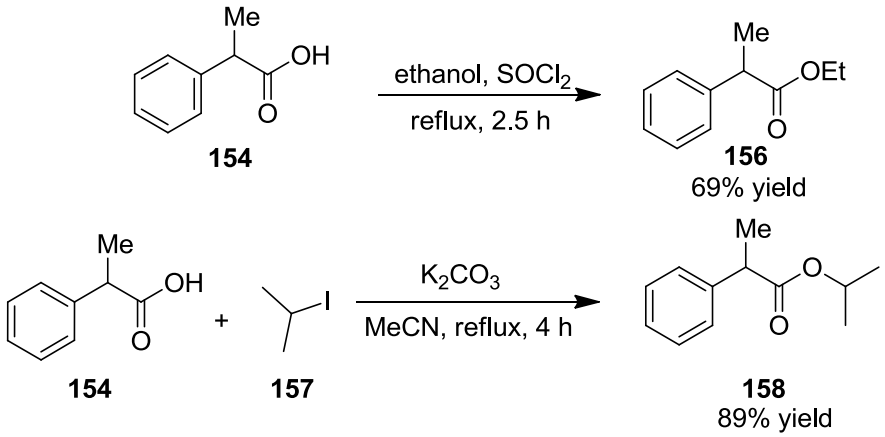
2-phenylpropanoic acid, using dimethyl carbonate and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) (Scheme 51).



154 **155** **15**
76% yield

Scheme 51. Esterification of 2-phenylpropanoic acid.

Ethyl 2-phenylpropanoate as well as isopropyl 2-phenylpropanoate were synthesized in the hope that they would either be more stable towards ester hydrolysis or sterically more hindered and thus give a better enantioselectivity than the methyl ester (Scheme 52).



154 **156**
69% yield

154 **157** **158**
89% yield

Scheme 52. Esterification of 2-phenylpropanoic acid.

As can be seen from the Bordwell table in chapter 2, the pK_a of our ester is expected to be between 18 and 25, which means that the reaction may follow the interfacial mechanism (Figure 8).

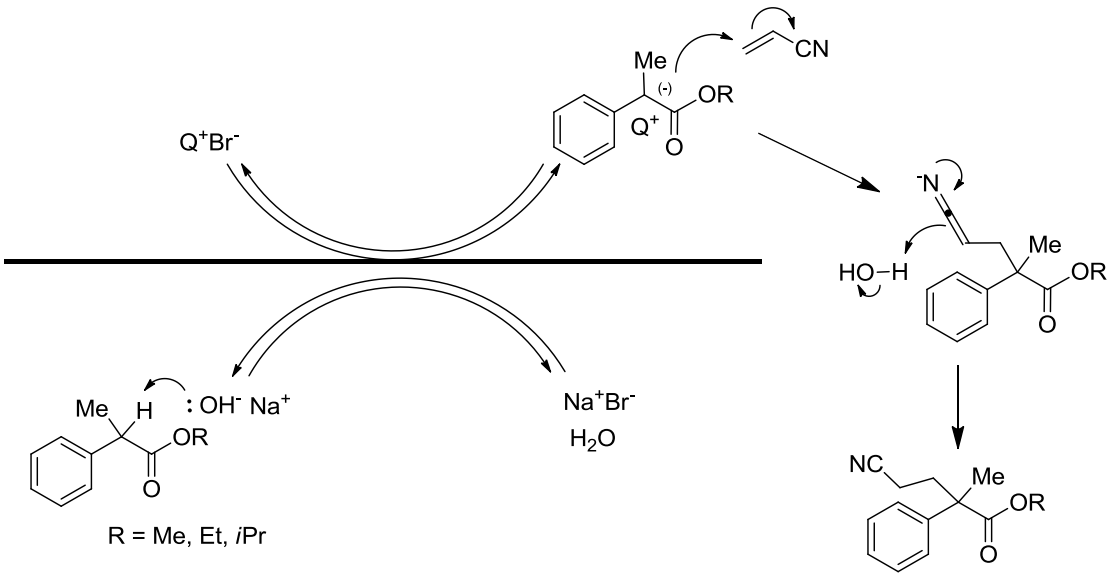
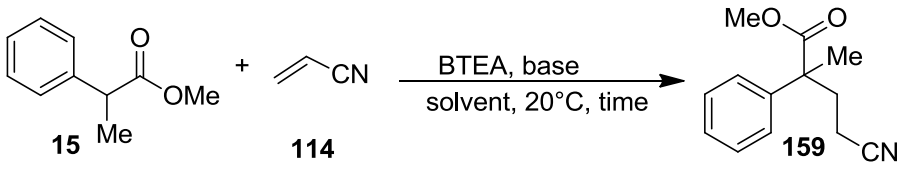


Figure 8. The expected mechanism for Michael addition of methyl 2-phenyl-propanoate to acrylonitrile.

4.2. Optimization

Once the starting material was available, the reaction conditions were sought after, and the synthesis of the racemate was attempted so that an enantioselectivity method could be established. Benzyltriethylammionium chloride (BTEA) was used as the catalyst in the synthesis of the racemate (Table 2).

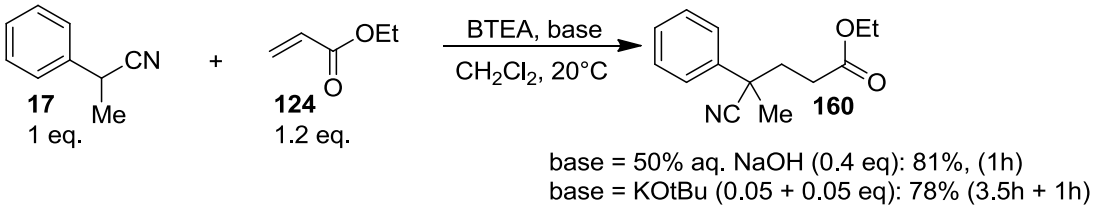
Table 2. Michael addition of methyl 2-phenylpropanoate to acrylonitrile[a].



Base		Catalyst amount	Solvent	t [h]	Yield [%]
KOtBu	0.05 eq	5 mol-%	CH_2Cl_2	25	-
KOtBu	0.05 eq	5 mol-%	Toluene	18	[b]
CsCO3	0.2 eq	10 mol-%	CH_2Cl_2	1	-
CsCO3	0.2 eq	10 mol-%	Toluene	1	-
NaOH (50%)	0.8+0.8 eq	10 mol-%	CH_2Cl_2	1+3.5	22

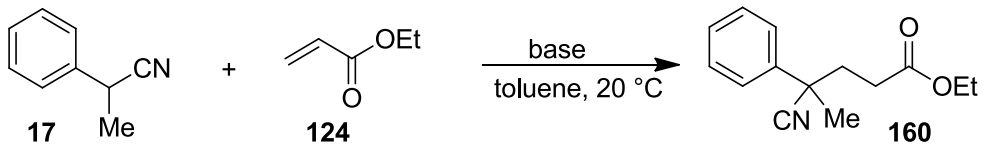
[a] Unless otherwise noted, the reaction was performed with 1.2 mmol of methyl 2-phenylpropanoate, 1.3 mmol of acrylonitrile and the above mentioned amount of base and catalyst in solvent (2 ml) at 20°C. [b] Small conversion, but product was lost due to purification issues.

Since the yield was minimal for the Michael addition of methyl 2-phenylpropanoate **15** to acrylonitrile **114**, we decided to investigate the Michael addition of α-methylbenzyl cyanide **17** to ethyl acrylate **124** (Scheme 53).



Scheme 53. Michael addition to phenylpropanenitrile.

This reaction was much faster and gave a better yield than the Michael addition of methyl 2-phenylpropanoate **15** to acrylonitrile **114**. According to the Bordwell's pK_a table in chapter 2 the difference between the pK_a of methyl 2-phenylpropanoate and α-methylbenzyl cyanide is small, but vital for this reaction to proceed as wished. Now that the starting material had been established the next step was making sure the background reactions would not overtake the catalyzed reaction. Not being sure which solvent was the optimal solvent, the background reaction rate was measured for both toluene (Figure 9) and dichloromethane (Figure 11) using UPLC-MS analysis.



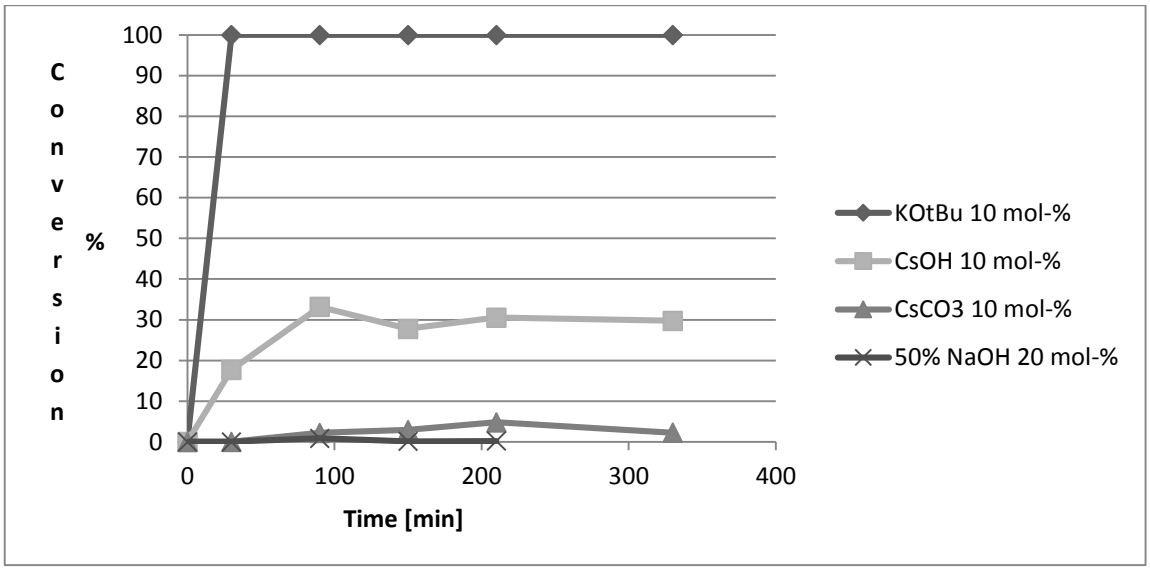


Figure 9. Background reaction rate in toluene over several hours using different bases.

Even with a large amount of 50% aqueous sodium hydroxide over several days at room temperature the background reaction would not interfere with the catalyzed reaction (Figure 10).

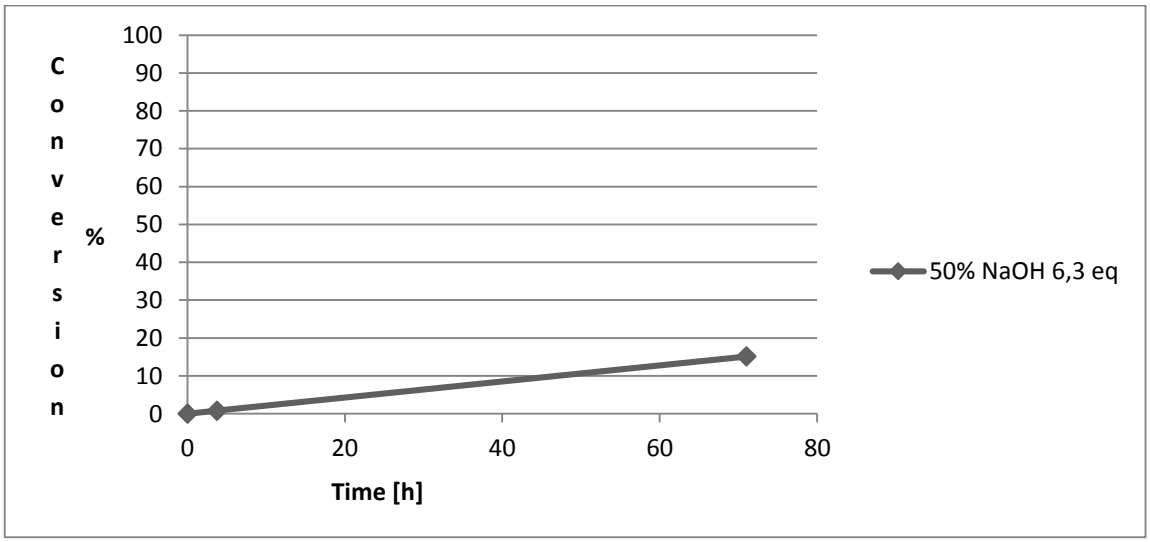


Figure 10. Background reaction rate in toluene over several days using a large amount of sodium hydroxide.

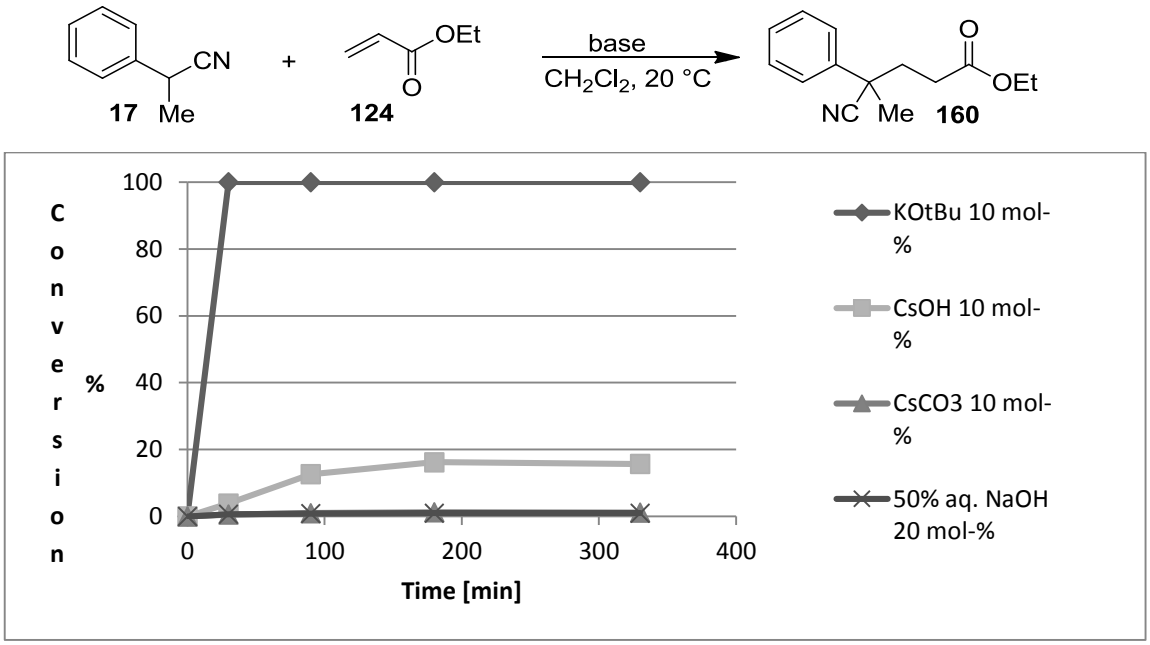


Figure 11. Background reaction rate in dichloromethane over several hours using different bases.

There were some concerns for autocatalysis due to the observation of a minimal amount of double addition of the intermediate enolate (Figure 12). The background reaction rates do not rule out autocatalysis, but they do not suggest autocatalysis either.

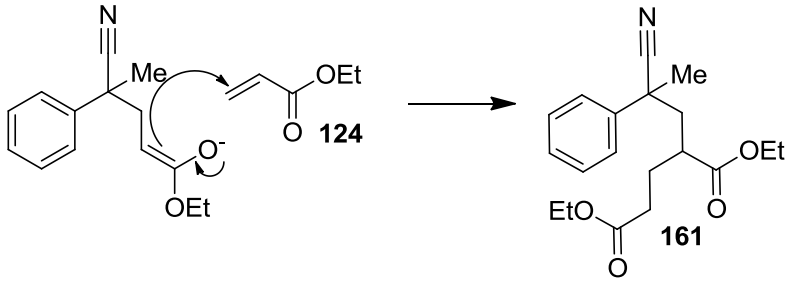
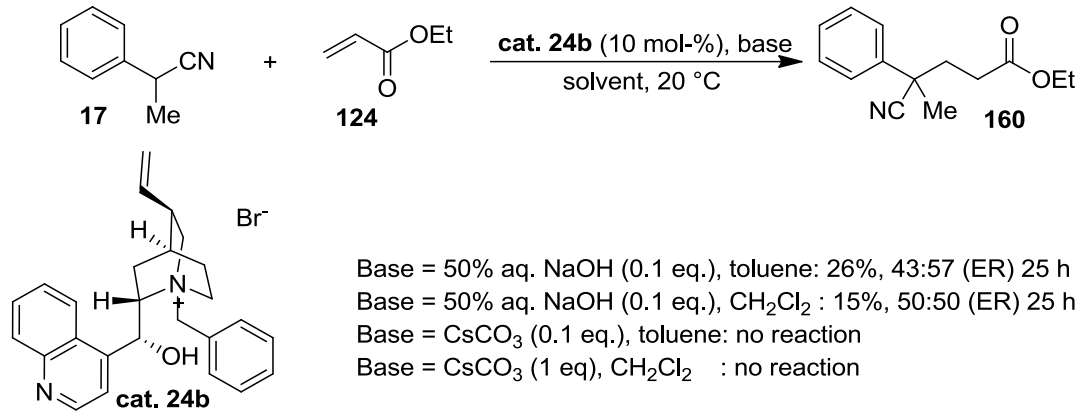


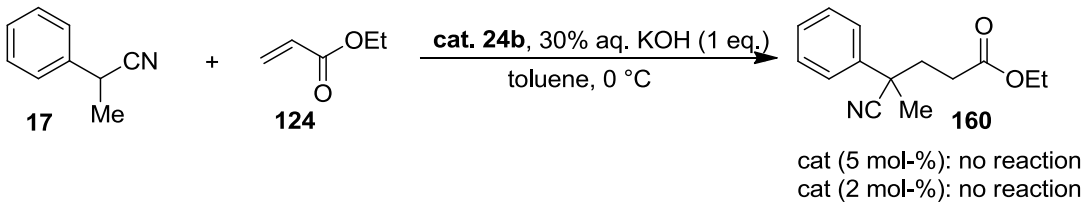
Figure 12. Double addition of the intermediate enolate.

The background reaction rate for potassium *tert*-butoxide was very high, and therefore potassium *tert*-butoxide could not be used as the base in the reaction. With enough cooling of the reaction mixture caesium hydroxide might be used and would be a good alternative at temperatures below the freezing point for aqueous base solutions. However, at room temperature, only caesium carbonate and aqueous sodium hydroxide would have an acceptable rate of background reactions (Scheme 54).



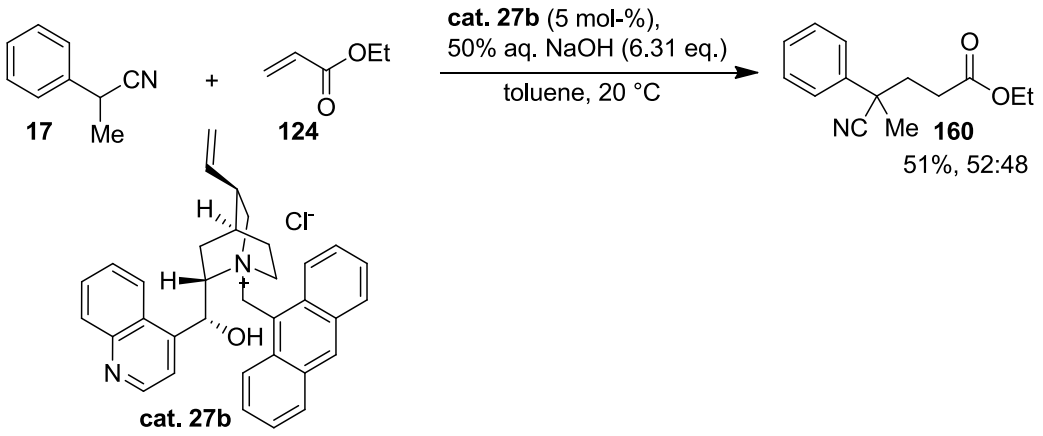
Scheme 54. *N*-benzylcinchonidinium bromide catalyzed Michael addition.

The results from the reactions above indicated that the basicity of caesium carbonate was not adequate for the reaction. When the same reaction was repeated using 1 equivalent of sodium hydroxide, but a small amount of distilled water was added to the reaction as well, thus lowering the concentration of the base, only a minimal conversion could be detected regardless of which solvent was used. The same effect could be detected when 30% aqueous potassium hydroxide was used (Scheme 55). Thus the conclusion that the concentration of the base used in the reaction was a vital part of Michael addition could be made.



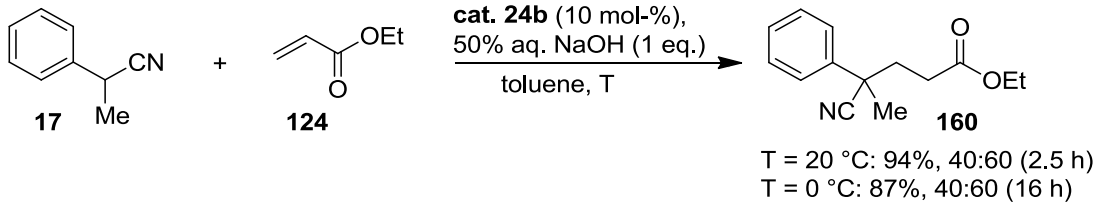
Scheme 55. Michael addition using potassium hydroxide as base.

Another observation made when the reaction was repeated using *N*-(9-anthracenyl-methyl)cinchonidinium chloride was that a large amount of base seems to hinder the reaction as well (Scheme 56).



Scheme 56. *N*-(9-anthracenylmethyl)cinchonidinium chloride catalyzed Michael addition.

When the concentration and the quantity limitations of the base were taken into account, the reaction conditions were adjusted to the following (Scheme 57):



Scheme 57. Adjusted reaction conditions.

However, no increase in the enantioselectivity could be observed when the temperature was dropped from 20°C to 0°C (Scheme 57). Now that the amount and concentration of the base had been adjusted to the optimal conditions, the next step was to choose the optimal catalyst and the optimal amount of catalyst. Since many *Cinchona* derived catalysts were commercially available and there was plenty of literature available about many, it was decided that the project would begin with an evaluation of a few of these. There are four main structures to choose from; cinchonidine which is enantio-complementary with cinchonine and quinine which is enantio-complementary with quinidine (Figure 13).

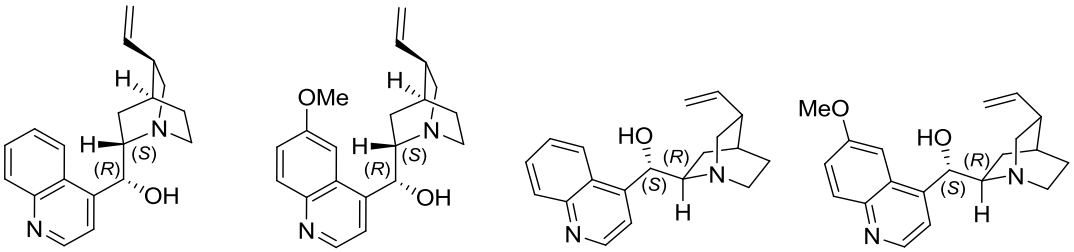
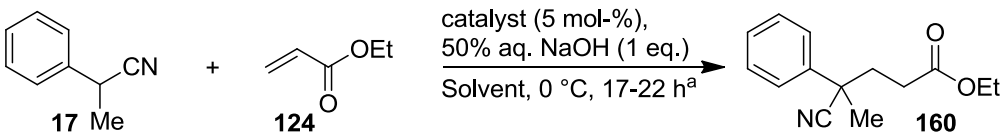
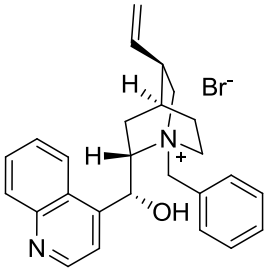
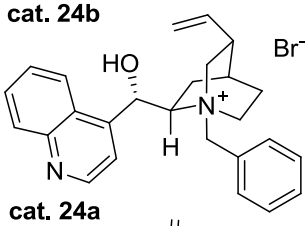
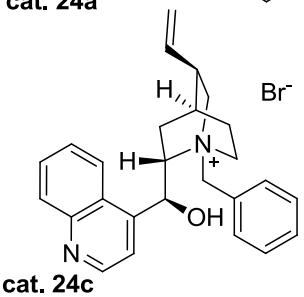
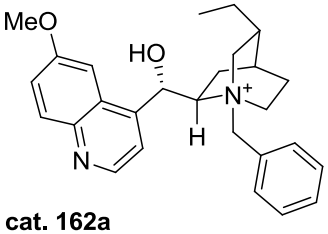


Figure 13. *Cinchona* alkaloid structures.

Denmark and Weintraub studied the catalyst structure-activity/selectivity relationships for *Cinchona* alkaloid-based asymmetric phase-transfer catalysis in 2011, and for their study they also created *epi*-cinchonidine, which could then be benzylated to the corresponding *N*-benzyl-*epi*-cinchonidinium bromide. [56] The epi-cinchonidine was included in our comparison between the main structures of the *Cinchona* alkaloids (Table 3).

Table 3. Comparison between the main *Cinchona* alkaloid structures.



Catalyst	Solvent	Yield (%)	ER (ee%)
 **cat. 24b**	Toluene	81%	39:61 (22% ee)
	CH_2Cl_2	85%	40:60 (20% ee)
 **cat. 24a**	Toluene	82%	54:46 (8% ee)
 **cat. 24c**	Toluene	76%	40:60 (20% ee)
 **cat. 162a**	Toluene	81%	45:55 (10% ee)

[a] Unless otherwise noted, the reaction was performed with 1.5 mmol of α-methylbenzyl cyanide, 2.0 mmol ethyl acrylate (1.3 eq), 1.5 mmol of 50% aqueous sodium hydroxide and 5 mol-% of catalyst in solvent (5 ml) at 0°C.

There seemed to be no significant difference between using dichloromethane and toluene for the reaction, so toluene was used as default in the following reactions in this thesis. Only in the case when the catalyst was insoluble in chloroform was

dichloromethane used for the reaction since it seemed to dissolve at least a small amount of the catalyst.

The results indicated that the optimal structure for further investigation would be cinchonidine or epi-cinchonidine, but since epi-cinchonidine is synthesized from cinchonidine and it did not give a better result than cinchonidine, it was decided that further investigation would be conducted using modified cinchonidine compounds only. It seems like the stereochemistry of C(9) does not play as a significant role as the rotation of the substituents at C(8) and other stereocenters at the quinuclidine group (Figure 14). The results obtained later in the project would be compared to the results obtained with the use of catalyst **24b**.

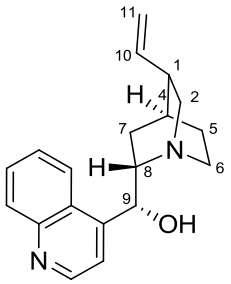


Figure 14. Numbering of carbons.

The chemical subunits that are thought to have an impact on the catalytical abilities of the *Cinchona* alkaloids are the quinoline, the secondary alcohol, the terminal alkene and the sterically hindered tertiary amine. The easily modified parts of the *Cinchona* alkaloid are the secondary alcohol and the tertiary amine (Figure 15).

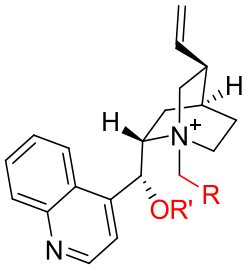
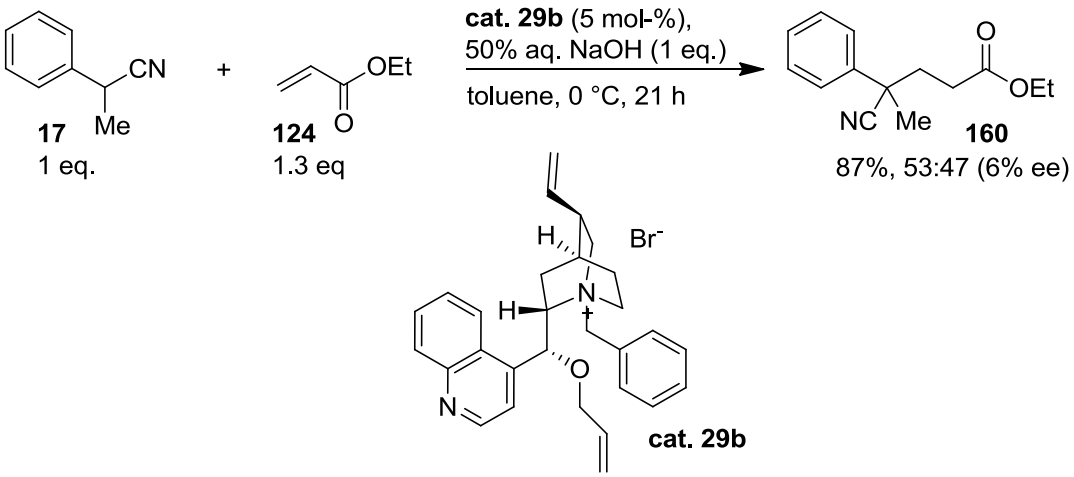


Figure 15. The easily modified parts of the *Cinchona* alkaloids.

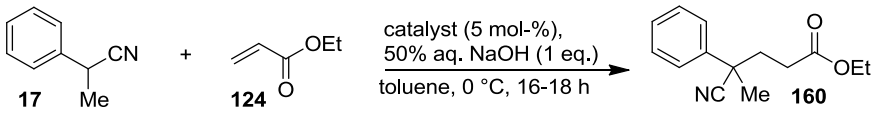
Many have found that when allylated the *Cinchona* alkaloid derived catalyst may provide higher optical purities than when not. [11,16] Thus, the first alteration to our *N*-benzylcinchonidinium bromide **24b** was to allylate the secondary alcohol (Scheme 58).

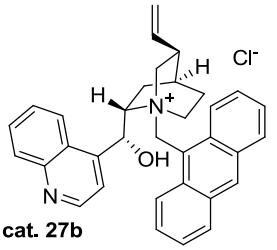
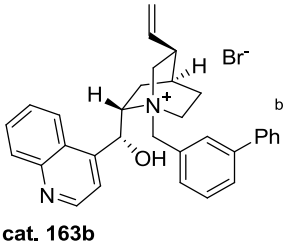
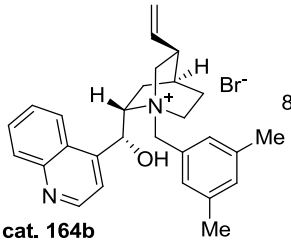
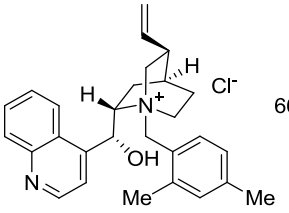
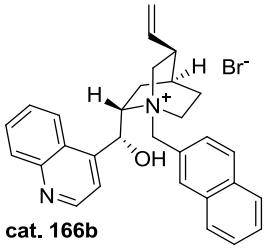
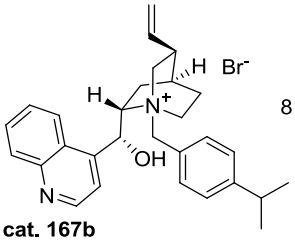


Scheme 58. *O*-allyl-*N*-benzylcinchonidinium bromide catalyzed Michael addition.

Unfortunately, the product was practically racemic when allowing for margin of error. Therefore, the only easily modified part left was the aryl attached to the tertiary amine. First the steric effects in *ortho, meta* and *para* positions of the aryl ring were investigated (Table 4).

Table 4. Comparison between sterically hindered cinchonidine compounds.[a]



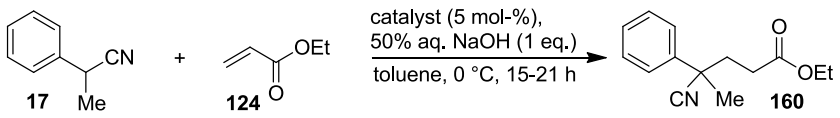
Catalyst	Yield (%)	ER	Catalyst	Yield (%)	ER
 cat. 27b	90%	50:50 (0% ee)	 cat. 163b	[b] 65%	42:58 (16% ee)
 cat. 164b	84%	39:61 (22% ee)	 cat. 165b	66%	37:63 (26% ee)
 cat. 166b	[b] 78%	41:59 (18% ee)	 cat. 167b	81%	45:55 (10% ee)

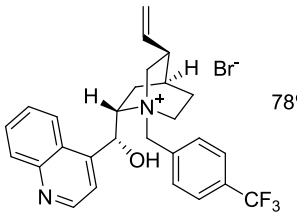
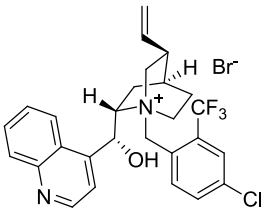
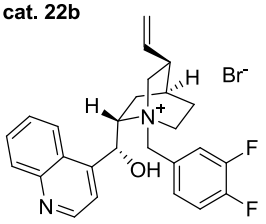
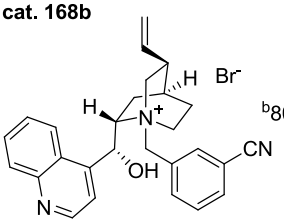
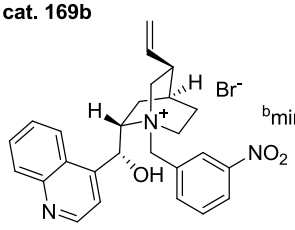
[a] Unless otherwise noted, the reaction was performed with 1.5 mmol of α-methylbenzyl cyanide, 2.0 mmol ethyl acrylate (1.3 eq), 1.5 mmol of 50% aqueous sodium hydroxide and 5 mol-% of catalyst in toluene (5 ml) at 0°C. [b] Dichloromethane used as solvent

Only catalyst **164b** and **165b** gave as good or minimally better enantioselectivities than catalyst **24b**. This means that all other substitutions lowered the enantioselectivity achieved by the catalyst. However, it is difficult to draw conclusions, since the difference is quite minimal between the catalysts. Catalyst **27b** gave a completely racemic product, meaning that big blades positioned sideways blocks the enantioselectivity providing part(s) of the catalyst. Catalyst **166b** only altered the enantioselectivity minimally, meaning that expanding the blade in that position has almost no impact on the reaction. Catalyst **167b** lowered the enantioselectivity substantially, suggesting that bulky substitutes at the *para*-position hinder the active

site(s) at the catalyst, while if the substitute is shifted to the meta-position (catalyst **163b**) it does not hinder the enantioselectivity as much. Since steric bulk did not aid the catalyst, the next area of interest was the electronic effect that could be provided by using fluorinated aryls, a nitro aryl or a nitrile aryl (Table 5).

Table 5. Comparison between electronically influenced cinchonidine compounds.[a]



Catalyst	Yield (%)	ER	Catalyst	Yield (%)	ER
 **cat. 22b**	78%	55:45 (10%ee)	 **cat. 168b**	79%	53:47 (6% ee)
 **cat. 169b**	83%	43:57 (14%ee)	 **cat. 170b**	[b]80%	37:63 (26% ee)
 **cat. 171b**	[b]minimal conversion, catalyst deteriorated				

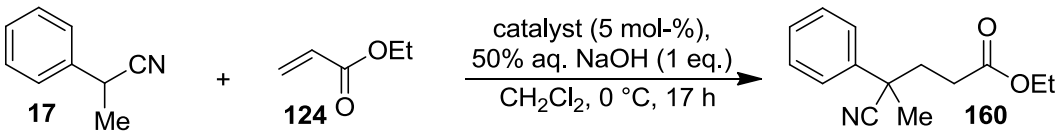
[a] Unless otherwise noted, the reaction was performed with 1.5 mmol of α-methylbenzyl cyanide, 2.0 mmol ethyl acrylate (1.3 eq), 1.5 mmol of 50% aqueous sodium hydroxide and 5 mol-% of catalyst in toluene (5 ml) at 0°C. [b] Dichloromethane used as solvent

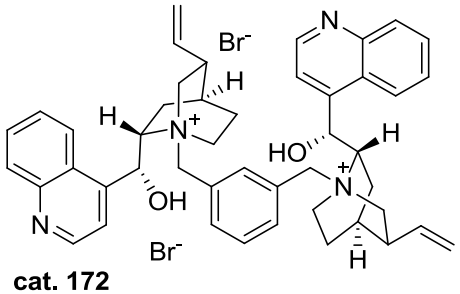
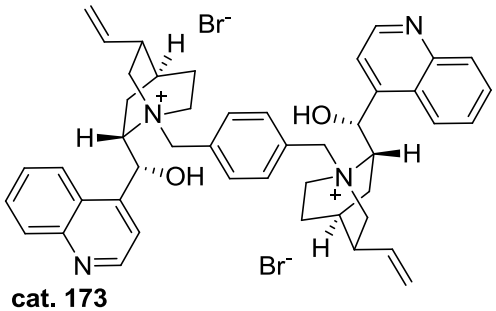
Interestingly enough, when a trifluoromethyl group is added to the benzyl substituent, it gives an enantiomeric excess of the other enantiomer compared to a similar catalyst with a carbon substitution in the same position, like catalyst **165b** and **167b**. But unlike in the report by Jew and co-workers, the addition of fluoro substituents did not

dramatically increase the enantioselectivity [17]. The nitrile substituted catalyst (catalyst **170b**) did minimally increase the enantioselectivity of the product and it was hoped that a more electronegative substituent at the meta-position might increase the enantioselectivity even further. Unfortunately no support for this hypothesis could be provided since the nitro substituted catalyst (catalyst **171b**) deteriorated almost instantly when added to the reaction.

The last *Cinchona* alkaloid-derived catalysts evaluated in the experimental part of this thesis were the dimeric *Cinchona* catalysts of Jew and co-workers [15]. Two dimeric cinchonidinium salts were prepared, related to those of Jew and co-workers, but unallylated since the *O*-allylated *N*-benzylcinchonidinium bromide **29b** provided us with a racemic product (Table 6).

Table 6. Comparison between dimeric *Cinchona* alkaloid derived catalysts.[a]



Catalyst	Yield (%)	ER (ee%)
 **cat. 172**	37%	36:64 (28% ee)
 **cat. 173**	63%	51:49 (2% ee)

[a] Unless otherwise noted, the reaction was performed with 1.5 mmol of α-methylbenzyl cyanide, 2.0 mmol ethyl acrylate (1.3 eq), 1.5 mmol of 50% aqueous sodium hydroxide and 5 mol-% of catalyst in dichloromethane (5 ml) at 0°C (reaction time 17 h).

Since the para-substituted catalyst **167b** decreased the enantioselectivity, it was not surprising that the para-dimeric catalyst **173** did not give rise to a more optically pure product. However, it was somewhat surprising that the meta-dimeric catalyst **172** increased the enantioselectivity in such a manner as it did when the result of catalyst **163b** is considered. It would have been interesting to study the effect of a 2-fluorosubstituted dimeric *Cinchona* catalyst on the reaction, but considering the yield and low enantioselectivity of the reaction catalyzed by catalyst **172**, it is unlikely that it would have provided a completely optically pure product.

The partition coefficients (LogP) were calculated and the distribution coefficient was measured (LogD) for some of the *Cinchona* alkaloid derived catalysts (Table 7). The distribution coefficients were measured at pH 7.4, which is the physiological pH of blood serum, and therefore the standard value at which the distribution coefficient is measured at this institution. Since the reaction is performed in a more basic solution, a logD measurement at pH 10-12 might have given a more realistic correlation to the enantioselectivity. The log D value for *N*-benzyldihydroquinidinium bromide (Figure 16) is comparable to that of the corresponding cinchonidine even though it lacks the vinyl and has a methoxy group on the quinoline. The methoxy group will make quinidine slightly more hydrophilic than the corresponding cinchonidine.

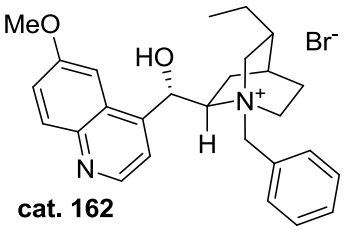
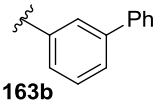
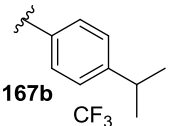
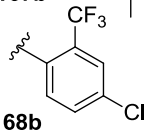
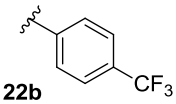
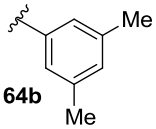
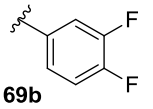
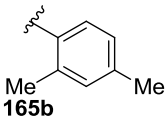
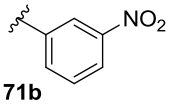
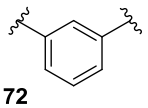
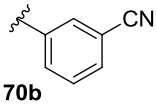
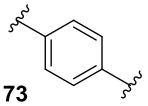
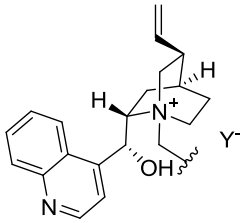
	Yield	ER (% ee)	LogD pH 7.4	LogP (Percepta)
 **cat. 162**	81%	45:55 (10% ee)	-0.09	-0.19

Figure 16. LogD and logP values for *N*-benzyldehydroquinidinium bromide.

Table 7. The measured and calculated logD value for some of the catalysts.

	Yield	ER (% ee)	LogD pH 7.4	LogP (Percepta)
 **cat. 163b**	65%	42:58 (16% ee)	1.30	0.64
 **cat. 167b**	81%	45:55 (10% ee)	0.83	0.29
 **cat. 168b**	79%	53:47 (6% ee)	0.72	0.78
 **cat. 22b**	78%	55:45 (10%ee)	0.61	0.29
 **cat. 164b**	84%	39:61 (22% ee)	0.42	0.06
 **cat. 169b**	83%	43:57 (14%ee)	0.00	-0.44
 **cat. 165b**	66%	37:63 (26% ee)	-0.01	0.06
 **cat. 171b**	minimal conversion, catalyst deteriorated		-0.56	-0.61
 **cat. 172**	[a]37%	36:64 (28% ee)	-0.67	<-2
 **cat. 170b**	80%	37:63 (26% ee)	-0.69	-0.66
 **cat. 173**	[a]63%	51:49 (2% ee)	-1.06	<-2



[a]Dimeric *Cinchona* alkaloid derived catalysts **172** and **173**

Interestingly a correlation between the enantioselectivity of the catalyst and the distribution of the catalyst between phases at pH 7.4 can be observed (Figure 17). To

be kept in mind is that the enantioselective is not solely dependent on the distribution between phases but that steric and electronic effects play a significant role in the matter. The dimeric catalysts cannot be compared to the other catalysts, but it seems that the more hydrophilic a compound is the more enantioselective it is. Based on the logD value for the *m*-nitrobenzyl catalyst **170b**, it would not have been more enantioselective than the *m*-cyanobenzyl, but because of the electronic effect provided by the electron withdrawing group, the nitrobenzyl might have provided for a better enantioselectivity.

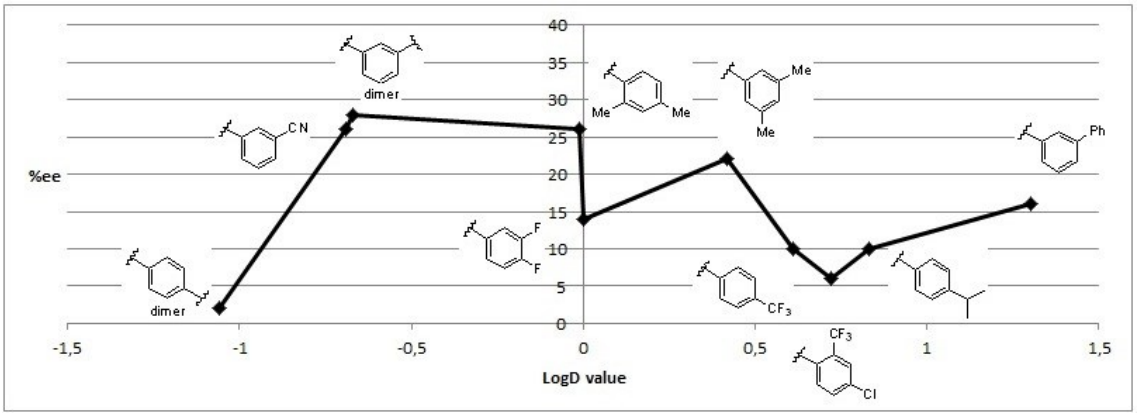
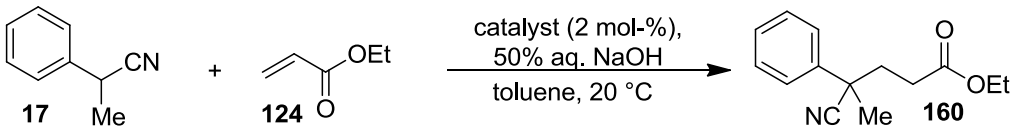
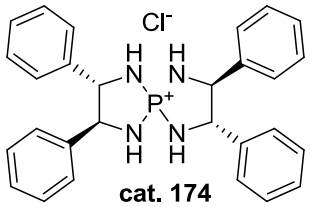
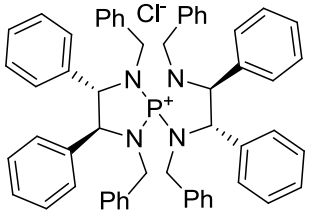
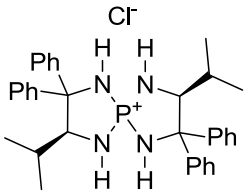


Figure 17. Correlation between LogD and the enantioselectivity at pH 7.4.

Satisfied that the *Cinchona* alkaloid derived catalysts had been investigated as far as this thesis would allow, the next category, namely the chiral tetraaminophosphonium salts of Ooi and co-workers were studied (Table 8).

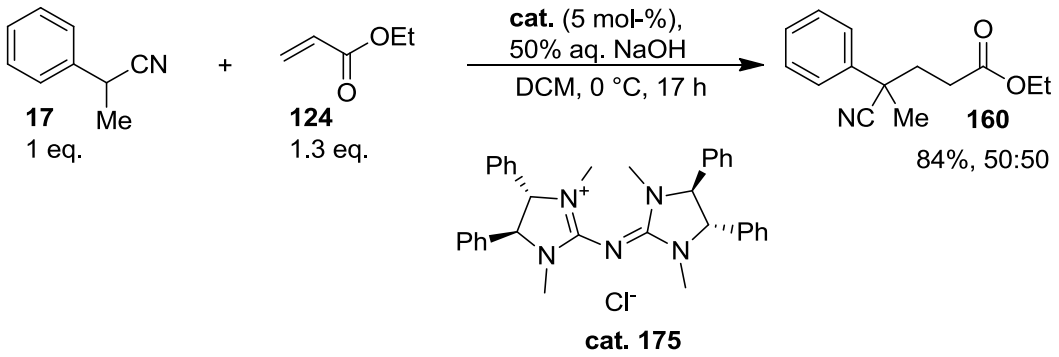
Table 8. Comparison of chiral tetraaminophosphonium chloride catalyzed Michael addition.



Catalyst	Yield (%)	ER (ee%)	time
 **cat. 174**	46%	50:50	94 h
 **cat. 65a**	[a]20%	50:50	2 h
 **cat. 45a**	13%	53:47 (6% ee)	23 h

[a] Reaction stalled after 2h, 1 eq of NaOH was added but no change could be detected.
[b] Unless otherwise noted, the reaction was performed with 1.5 mmol of α-methylbenzyl cyanide, 2.0 mmol ethyl acrylate (1.3 eq) and 1.5 mmol of 50% aqueous sodium hydroxide and 2 mol-% of catalyst in toluene (5 ml) at 20°C.

The chiral tetraaminophosphonium salts developed by Ooi and co-workers did not catalyze in an enantioselective way, so further investigation in this area was deemed unnecessary. Guanidines are not basic enough structures for the reaction aimed at in this thesis, so instead it was decided that the pentanidium salt created by Tan and co-workers would be investigated (Scheme 59).

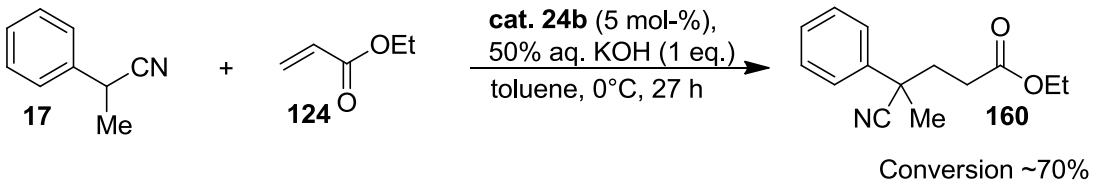


Scheme 59. Pentanidium chloride catalyzed Michael addition.

Unfortunately the pentanidium catalyst also gave a racemic product so further evaluation of this category was also deemed unnecessary.

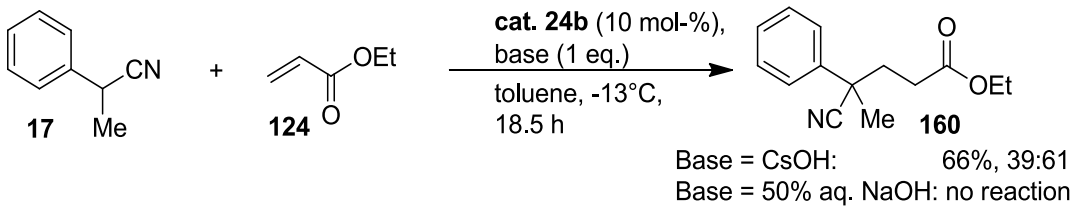
4.3. Attempting to improve the enantioselectivity

Accepting that the best results in this thesis were obtained with cinchonidine salts, we attempted to improve the enantioselectivity by lowering the reaction temperature to –13°C (as low as the overnight equipment would allow). Since the theoretical freezing point for 50% aqueous sodium hydroxide is about 12°C and for 50% aqueous potassium hydroxide about 5°C, it would have been convenient to change the base used. However, when the potassium hydroxide was used the full conversion usually observed with sodium hydroxide did not occur, instead the conversion never reached above 70% (approximation based on UPLC-MS measuring, 210 nm) (Scheme 60).



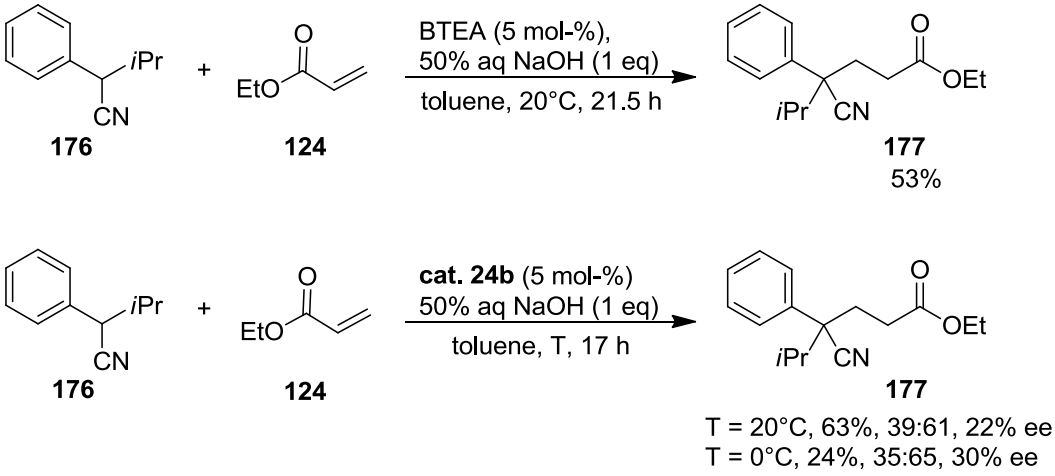
Scheme 60. Potassium hydroxide used as base in the Michael addition.

As earlier mentioned caesium hydroxide in its solid form was a valid option as long as the reaction mixture was cold enough. Therefore, in the next experiment, caesium hydroxide was used (Scheme 61). As expected the sodium hydroxide in the parallel experiment was made inactive by being frozen. Unfortunately the temperature change did not improve the enantioselectivity.



Scheme 61. Michael addition at -13°C.

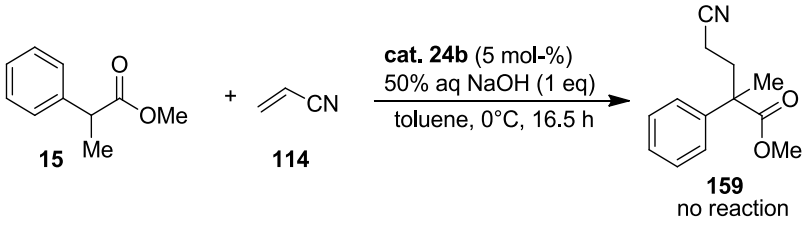
Another attempt to increase the enantioselectivity was made by increasing the steric bulk of the benzyl cyanide. This was done by replacing the methyl group in **17** with an isopropyl group (Scheme 62).The enantioselectivity was increased slightly, from 22% ee to 30% ee for the corresponding reaction.



Scheme 62. Michael addition of α-isopropylbenzyl cyanide to ethyl acrylate.

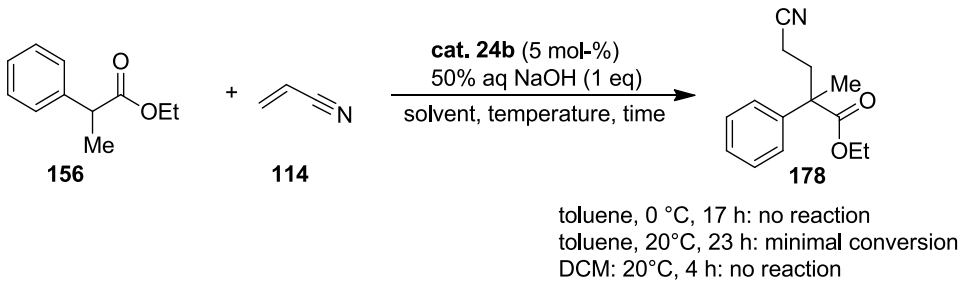
4.4. Other phase-transfer catalyzed Michael additions

Now when the optimal reaction conditions were known, a return to the original concept was attempted only this time using methyl ester, ethyl ester and propyl ester. No reaction could be observed for the methyl ester **15** (Scheme 63).



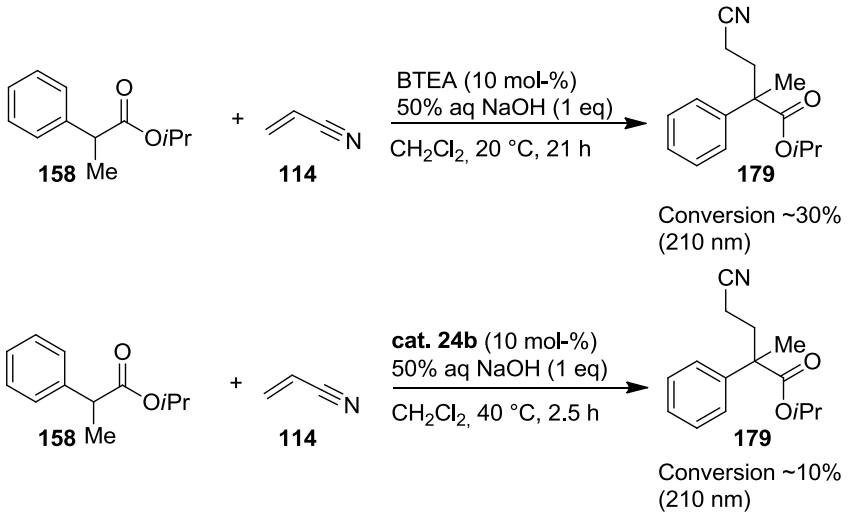
Scheme 63. Michael addition of methyl 2-phenylpropanoate to acrylonitrile.

The Michael addition of ethyl 2-phenylpropanoate to acrylonitrile was attempted both in room temperature and at 0°C (Scheme 64).



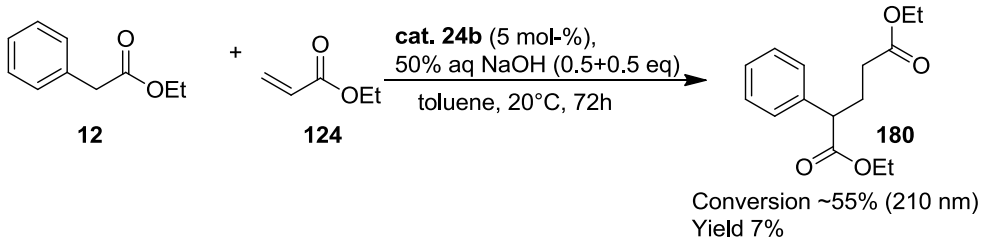
Scheme 64. Michael addition of ethyl 2-phenylpropanoate to acrylonitrile.

A small conversion (UPLC-MS based estimation) for the propyl ester could be observed, but it was not substantial enough for us to attempt to isolate the product (Scheme 65).



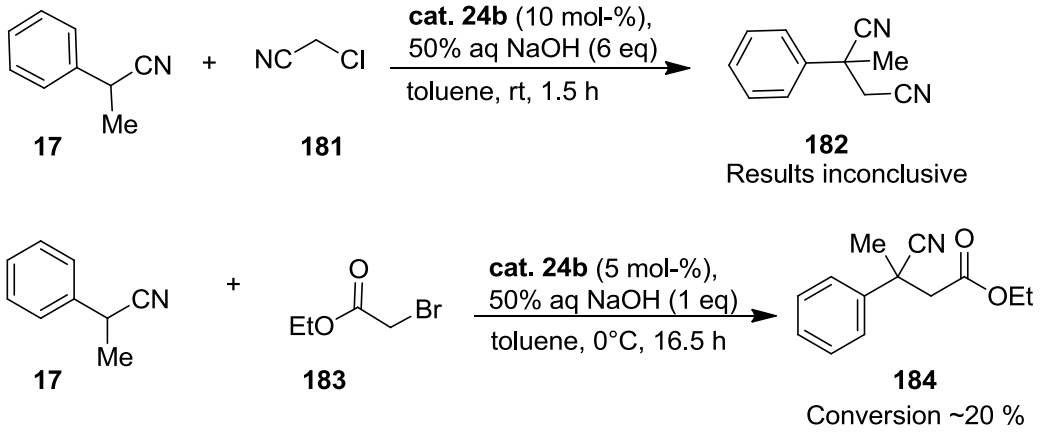
Scheme 65. Michael addition of isopropyl 2-phenylpropanoate to acrylonitrile.

A version of the Cram and Sogah reaction (Scheme 27) using the *N*-benzylcinchonidinium bromide **24b** as catalyst instead of chiral crown ethers. The methyl 2-phenylpropanoate was substituted for ethyl 2-phenylacetate and methyl acrylate was substituted for ethyl acrylate, in the hopes that they could withstand possible hydrolysis a bit better than the corresponding methyl esters. The conversion (UPLC-MS based estimation) reached 55%, but in the isolation most of the product must have been lost, since the acquired yield was only 7% (Scheme 66). This is believed to have occurred due to hydrolysis.



Scheme 66. Synthesis of diethyl 2-phenylpentanedioate.

The following reactions were also attempted but for the first reaction the results were inconclusive, while for the second one, it seems that the ethyl bromoacetate reacts with the catalyst, thus lessening the available amount of reagent for the reaction as well as altering the catalyst (Scheme 67).



Scheme 67. Alkylation using chiral phase-transfer catalysts.

4.5. Conclusions

Since the era of chiral crown ethers a large number of naturally occurring alkaloid derivatives have been elaborated as powerful and readily available chiral phase-transfer catalysts as well as a large number of purely synthetic chiral quaternary onium salts have been developed. Three categories of phase-transfer catalysts were chosen for evaluation; unfortunately none of the catalysts evaluated in this thesis provided an enantioselectivity comparable to chiral crown ethers for the Michael additions aimed at in this thesis. The optimal reaction conditions were successfully created for the Michael addition of α-methylbenzyl cyanide to ethyl acrylate, but a catalyst which could provide for satisfactory enantioselectivity was not found for this reaction.

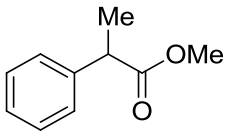
5. Experimental

5.1. Experimental procedures

Solvents and commercial reagents were purchased from commercial sources and used without purification. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker Avance 400 MHz spectrometer and chemical shifts are reported in ppm. LC-MS reaction monitoring data were recorded on a combination of Waters Acquity UPLC and Waters SQ mass detector, using a gradient of MeCN / HCO_2H (0.1%) as eluent. The enantiopurity was measured with an Agilent HPLC 1200, Agilent HPLC 1100 and an Acquity UPC2 SFC, examples of typical spectra are provided in Appendix 16 and 17. The HRMS was measured with a Waters Micromass Premier Q-TOF. The distribution coefficients were calculated using ACD/Percepta, and measured using the shake flask method. For purification of products normal phase flash column chromatography was performed on a Teledyne Isco CombiFlash Rf+ with RediSep Rf silica columns and eluent of choice.

5.2. Synthesis of starting materials

Methyl-2-phenylpropanoate 15



In a 50 ml round-bottomed flask 2-phenylproprionic acid (2.66 ml, 19.48 mmol) was diluted with dimethyl carbonate (25 ml, 297 mmol, 14.85 eq). 1,8-diazabicyclo(5,4,0)undec-7-ene (2.99 ml, 19.98 mmol, 1 eq) was added to the solution in a portion wise manner. The reaction mixture was refluxed until judged to be complete (approximately 10 h). The reaction mixture was cooled to room temperature and diluted with 20 ml of ethyl acetate and 20 ml of distilled water. The phases were separated and the organic phase was washed with distilled water (25 ml), 2 M hydrochloric acid aqueous solution (2 x 20 ml), saturated sodium hydrogen carbonate (2 x 20ml) and distilled water (3 x 25 ml). The organic phase was dried over sodium sulfate and solvents were evaporated. The crude product was purified by flash column

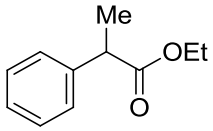
chromatography using heptane and ethyl acetate as eluents. The product attained was a colorless liquid (2.51 g, 76%).

Methyl 2-propanoate was prepared according to the procedure reported by W.-C. Shieh and co-workers. [57]

^{1}H NMR ($CDCl_3$, 400 MHz) δ ppm 7.37 - 7.21 (m, 5H), 3.72 (q, *J* = 7.2 Hz, 1H), 3.66 (s, 3H), 1.50 (d, *J* = 7.2 Hz, 1H).

The ^{1}H NMR results corresponded to those reported in literature. [58]

Ethyl 2-phenylpropanoate 156



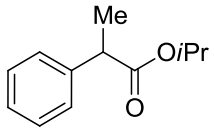
Ethanol (30 ml, 514 mmol, 25.7 eq) was cooled to about 0ºC in a 100 ml three-necked flask under a nitrogen atmosphere, equipped with a gas cleanser apparatus placed in an ice bath. Thionyl chloride (4.39 ml, 59.9 mmol, 3 eq) was added drop wise to the ethanol and the mixture was stirred for 30 minutes on the ice bath. 2-Phenylpropionic acid (2.73 ml, 19.98 mmol) was added to the mixture in a drop wise manner. The reaction mixture was refluxed at 95ºC until judged to be complete, which was approximately after 2.5 h of refluxation. The reaction mixture was cooled to room temperature and the solvents were evaporated. The remainder was dissolved in ethyl acetate and sodium hydrogen carbonate was added dropwise to the mixture until no further generation of gas could be detected. Phases were separated and the organic phase was washed with brine and dried over sodium sulfate. Solvents were evaporated and the crude product was purified by flash column chromatography using ethyl acetate and heptane (0-100%) as eluent. The purification afforded 2.46 g (69%) of very lightly yellow-tinted liquid.

Ethyl 2-propanoate was prepared according to the procedure reported by J.-E. Bäckvall and co-workers with some minor variations. [59]

^{1}H NMR ($CDCl_3$, 400 MHz) δ ppm 7.36 - 7.21 (m, 5H), 4.19 - 4.05 (m, 2H), 3.70 (q, *J* = 7.2 Hz, 1H), 1.52 - 1.48 (d, *J* = 7.2 Hz, 1H), 1.20 (t, *J* = 7.1 Hz, 1H).

The ^{1}H NMR results corresponded to those reported in literature. [60]

Isopropyl 2-phenylpropanoate 158

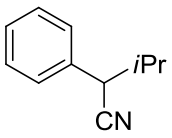


In a 100 ml round-bottomed flask equipped with a magnetic stirring bar 1.52 g (10.99 mmol, 150 mol%) of potassium carbonate was added to 40 ml of acetonitrile. To this heterogeneous mixture 1.00 ml (7.32 mmol, 100 mol%) of 2-phenylproprionic acid was added in a drop wise manner, followed by 0.88 ml (8.79 mmol, 120 mol%) of 2-iodopropane. The reaction was stirred at room temperature for 4.5 hours. Since no significant progress could be detected, the round-bottomed flask was equipped with a reflux condenser and the reaction mixture was refluxed for 1.5 hours. The reaction mixture was stirred overnight at room temperature and because the reaction had not completed, 5 ml of acetonitrile was added to the reaction mixture and it was refluxed for 2 hours. The remaining iodopropane had evaporated during the reflux so, 0.35 ml (0.5 eq) was added so that the reaction could complete. The reaction mixture was refluxed for 2 hours more. The reaction was considered to have completed, so solvents were evaporated from the mixture and saturated sodium bicarbonate solution was added to the remainder. The resulting mixture was extracted twice with ethyl acetate. The combined organic phases were washed with brine and dried over sodium sulfate. Solvents were evaporated yielding a yellow oil (m_{crude}=1.39 g). The yellow crude product was dissolved in dichloromethane and evaporated onto silica. The crude product was purified by flash column chromatography using a 40 g silica column and methyl *tert*-butyl ether and heptane as eluent. Solvents were evaporated from the fractions containing the product to afford a colorless oil (1.26 g, 89%).

^{1}H NMR ($CDCl_3$, 400 MHz) δ ppm 7.34 - 7.20 (m, 5H), 4.99 (spt, *J* = 6.3 Hz, 1H), 3.67 (q, *J* = 7.2 Hz, 1H), 1.50 - 1.46 (m, 3H), 1.22 (d, *J*=6.3 Hz, 2H), 1.13 (d, *J*=6.3 Hz, 1H).

The ^{1}H NMR results corresponded to those reported in literature. [61]

Isopropyl cyanide 176



To a 100 ml round-bottomed flask benzylcyanide (5 ml, 43.3 mmol, 100 mol%), 2-bromopropane (4.5 ml, 47.9 mmol, 110 mol%) and tetrabutylammonium bromide (0.279g, 0.866 mmol, 2 mol%) was added. The mixture was stirred vigorously before the drop wise addition of 60% potassium hydroxide (20.25 g, 217 mmol, 500 mol%). The reaction was heated to 45 ºC and stirred vigorously until judged to be complete, approximately 5 h after initiation. The reaction mixture was cooled to room temperature and 10 ml of distilled water as well as 10 ml dichloromethane were added and the phases were separated. The organic phase was washed with 20 ml of distilled water. The combined aqueous phases were extracted with dichloromethane (2 x 20 ml). The combined organic phases were washed with brine and dried over sodium sulfate. The crude product was purified by vacuum distillation, affording **176** (5.37 g, 78 %).

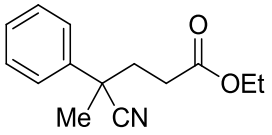
Isopropyl 2-propanoate was prepared according to the procedure reported by M. Fedoryński and co-workers. [62]

^{1}H NMR ($CDCl_3$, 400 MHz) δ ppm 7.41 - 7.27 (m, 5H), 3.66 (d, *J*=6.3 Hz, 1H), 2.20 - 2.07 (m, 1H), 1.08 - 1.01 (m, 6H)

The ^{1}H NMR results corresponded to those reported in literature. [63]

5.3. Products

Ethyl 4-cyano-4-phenylvalerate 160



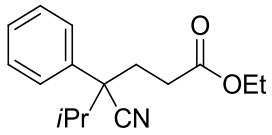
To a suitable round-bottomed flask equipped with a magnetic stirring bar the catalyst of choice (2-5 mol-%) was added to the solvent of choice (0.3 M). The base (100 mol-%) was added to the mixture under vigorous stirring. In the case of cooling, the reaction mixture was placed under a nitrogen atmosphere. α-Methylbenzyl cyanide **17** (0.20 ml, 1.50 mmol, 100 mol-%) was added to the reaction mixture in a dropwise manner. The reaction mixture was stirred for 15 minutes before ethyl acrylate **124** (0.21 ml, 1.95 mmol, 130 mol-%) was added to the reaction mixture. The reaction was monitored using UPLC-MS analysis and stirred until judged to be complete. The reaction mixture was subsequently quenched with brine and phases were separated. In the case of emulsions, the organic phase was washed twice more with brine and the combined aqueous phases were extracted once with dichloromethane. The combined organic phases were dried over Na_2SO_4 and solvents were evaporated. The crude product was purified by flash column chromatography using a suitable silica column and methyl *tert*-butyl ether and heptane (0-10%) as eluent.

^{13}C NMR ($CDCl_3$, 400 MHz) δ ppm 172.3, 139.2, 129.2, 128.2, 125.6, 122.8, 60.8, 42.1, 36.9, 30.7, 28.0, 14.3.

^{1}H NMR ($CDCl_3$, 400 MHz) δ ppm 7.46-7.30 (m, 5H), 4.14-4.01 (m, 2H), 2.53-2.44 (m, 2H), 2.36-2.25 (m, 2H), 2.24-2.15 (m, 1H), 1.75 (s, 3H), 1.22 (t, *J* = 7.1 Hz, 3H).

HRMS (Q-TOF): *m/z* calculated for $C_{14}H_{18}NO_2$ [M+H] 232.1338, found: 232.1337.

Ethyl 4-cyano-5-methyl-4-phenylhexanoate 177

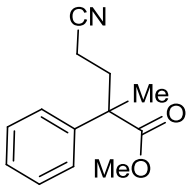


The catalyst (0.08 mmol, 5 mol-%) was added to a suitable round-bottomed flask equipped with a magnetic stirring bar containing toluene (0.3 M). 50% aqueous sodium hydroxide (0.080 ml, 1.51 mmol, 100 mol-%) was added to the mixture under vigorous stirring. In the case of cooling, the reaction mixture was placed under a nitrogen atmosphere. α-Isopropylbenzyl cyanide **176** (0.24 g, 1.51 mmol, 100 mol-%) was added to the reaction mixture in a dropwise manner. The reaction mixture was stirred for 15 minutes before ethyl acrylate **124** (0.21 ml, 1.96 mmol, 130 mol-%) of was added to the reaction mixture. The reaction was monitored using UPLC-MS analysis and stirred until judged to be complete. The reaction mixture was subsequently quenched with brine and phases were separated. The organic phase was washed twice more with brine and the combined aqueous phases were extracted once with dichloromethane. The combined organic phases were dried over Na_2SO_4 and solvents were evaporated. The crude product was purified by flash column chromatography using a suitable silica column and methyl *tert*-butyl ether and heptane (0-10%) as eluent. The product obtained was a colorless liquid.

^{1}H NMR ($CDCl_3$, 400MHz) δ ppm 7.42 - 7.35 (m, 4H), 7.35 - 7.27 (m, 1H), 4.12 - 3.99 (m, 2H), 2.55 - 2.33 (m, 2H), 2.24 - 2.10 (m, 2H), 2.00-1.89 (m, 1H), 1.27 - 1.17 (m, 6H), 0.79 (d, *J* = 6.8 Hz, 3H).

The ^{1}H NMR results corresponded to those reported in literature. [64]

Methyl 4-cyano-2-methyl-2-phenylbutanoate 159



The catalyst of choice (5-10 mol-%) was added to the solvent of choice (0.6 M) in a suitable round-bottomed flask equipped with a magnetic stirring bar. The base of choice (5–80 mol-%) was added to the mixture under vigorous stirring. α-Methyl 2-

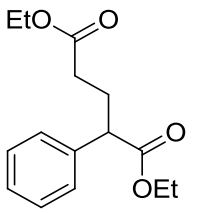
phenylpropanoate **15** (0.20 g, 1.22 mmol, 100 mol-%) was added to the reaction mixture in a dropwise manner. The reaction mixture was stirred for 15 minutes before acrylonitrile **114** (0.09 ml, 1.34 mmol, 110 mol-%) was added to the reaction mixture. The reaction was monitored using UPLC-MS analysis and stirred until judged to be complete. The reaction mixture was subsequently quenched with brine and phases were separated. The aqueous phase was extracted thrice with dichloromethane. The combined organic phases were dried over Na_2SO_4 and solvents were evaporated. The crude product was purified by flash column chromatography using a suitable silica column and methyl *tert*-butyl ether and heptane (0–10%) as eluent.

^{13}C NMR ($CDCl_3$, 400 MHz) δ ppm 175.6, 141.3, 129.0, 127.7, 125.9, 119.7, 52.6, 49.8, 35.6, 22.4, 13.3.

^{1}H NMR ($CDCl_3$, 400 MHz) δ ppm 7.39-7.21 (m, 5H), 3.70 (s, 3H), 2.38-2.13 (m, 4H), 1.63 (s, 3H).

HRMS (Q-TOF): *m/z* calculated for $C_{13}H_{16}NO_2$ [M+H] 218.1181, found: 218.1180.

Diethyl 2-phenylpentanedioate 181



N-benzylcinchonidinium bromide **24b** (0.02 g, 0.05 mmol, 5 mol-%) was added to 3 ml of toluene in a 10 ml round-bottomed flask equipped with a magnetic stirring bar. 50% aqueous sodium hydroxide (0.02 ml, 0.46 mmol, 50 mol-%) was added to the mixture under vigorous stirring followed by ethyl phenylacetate **12** (0.15 ml, 0.91 mmol, 100 mol-%). The reaction mixture was stirred for 5 minutes before ethyl acrylate **124** (0.10 ml, 0.91 mmol, 100 mol-%) was added to the reaction mixture. The reaction mixture was stirred for 3 h. UPLC-MS results indicated that the reaction had stopped, so 0.02 ml of 50% sodium hydroxide (0.46 mmol, 0.5 eq) was added to the reaction mixture. The reaction mixture was stirred for 69 h, but no significant progress could be detected. The reaction mixture was quenched with 5 ml of brine and phases were separated. The organic phase was washed with brine (3 x 5 ml), and the combined aqueous phases were extracted with dichloromethane. The combined organic phases were dried over Na_2SO_4 and solvents were evaporated. The crude product was

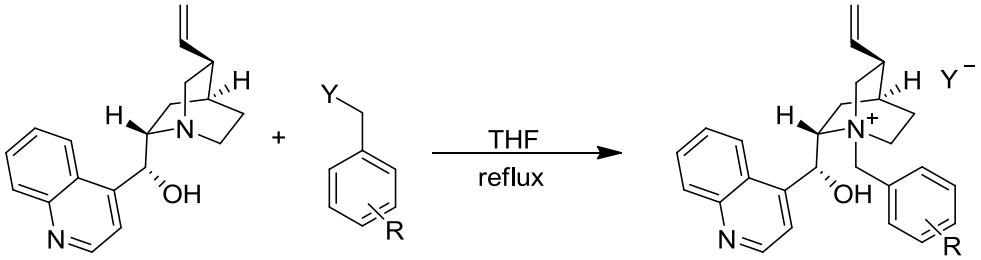
purified by flash column chromatography using a 4g silica column and methyl *tert*-butyl ether and heptane (0-10%) as eluent. 0.02 g of colorless liquid was obtained in a yield of 6.92%.

^{13}C NMR ($CDCl_3$, 400 MHz) δ ppm 173.6, 173.0, 138.5, 128.8, 128.1, 127.5, 61.0, 60.5, 50.8, 32.1, 28.6, 14.3, 14.2.

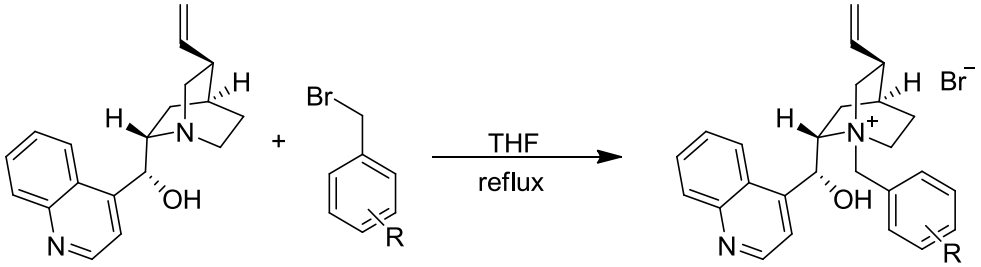
^{1}H NMR ($CDCl_3$, 400 MHz) δ ppm 7.35-7.23 (m, 5H), 4.20-4.04 (m, 4H), 3.60 (t, *J* = 7.6 Hz, 1H), 2.42-2.31 (m, 1H), 2.29-2.22 (m, 2H), 2.17-2.06 (m, 1H), 1.22 (dt, *J* = 14.7, 7.2 Hz, 6H).

HRMS (Q-TOF): *m/z* calculated for $C_{15}H_{20}O_4Na$ [M+Na] 287.1259, found: 287.1259.

5.4. Catalysts

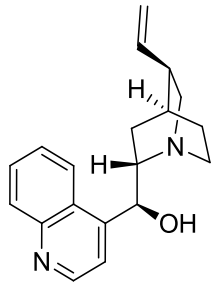


General Procedure I: To a flask equipped with a magnetic stirring bar and a reflux condenser the desired *Cinchona* alkaloid (cinchonidine, cinchonine, dehydroquinidine or epi-cinchonidine) (100 mol-%) was added, as well as dry THF (0.1 M), and the desired benzyl bromide or benzyl chloride derivative (100 mol-%). The mixture was heated to reflux until judged to be complete by LC-MS-analysis. The mixture was then cooled to room temperature and MTBE was added (twice the amount of THF). The resulting suspension was stirred for at least 1h and the precipitated solids were isolated by filtration. The product in question was dried in a vacuum oven at 40°C overnight.



General Procedure II: To a flask equipped with a magnetic stirring bar and a reflux condenser cinchonidine (100 mol-%) was added, as well as dry THF (0.1 M), and the desired benzyl bromide derivative (110 mol-%). The mixture was heated to reflux until judged to be complete by LC-MS-analysis. The mixture was then cooled to room temperature and MTBE was added (twice the amount of THF). The resulting suspension was stirred for at least 1h and the precipitated solids were isolated by filtration. The product in question was dried in a vacuum oven at 40 °C overnight.

Epi-cinchonidine



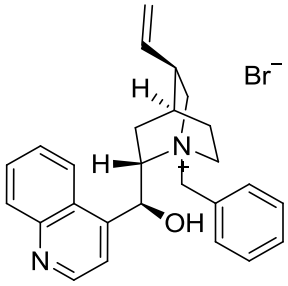
Epi-cinchonidine was prepared according to the procedure reported by Denmark and co-workers with some minor variations. [56]

Cinchonidine (2.94 g, 10 mmol, 100 mol-%), triphenylphosphine (2.89 g, 11.00 mmol, 110 mol-%) and 4-nitrobenzoic acid (5.18 g, 31.0 mmol, 310 mol-%) were dissolved in dry tetrahydrofuran (125 ml, 0.08 M) in a 250 ml three-necked round-bottomed flask under a nitrogen atmosphere. The resulting mixture was cooled in an ice-bath. Diisopropyl azodicarboxylate (2.2 ml, 11.17 mmol, 110 mol-%) was added to the mixture in a drop wise manner. The reaction mixture was stirred for one hour at 2-5ºC then allowed to warm to room temperature under the course of 1.5 h. The reaction mixture was diluted with methyl *tert*-butyl ether (50 ml) and extracted with 1 N hydrochloric acid aqueous solution (3 x 50 ml). The pH of the combined aqueous phases was raised using solid potassium carbonate to a pH of 9. The resulting solution was extracted with methyl tert-butyl ether (3 x 50 ml) then once using dichloromethane (50 ml). The combined organic extracts were dried over sodium sulfate and solvents were evaporated. The crude product was purified by flash column chromatography using methanol and dichloromethane (0-20%). The product was further purified by recrystallization from 2-propanol affording the product as an oil (1.34 g, 46%).

^{1}H NMR ($CDCl_3$, 400 MHz) δ ppm 8.77 (d, *J* = 4.5 Hz, 1H), 8.07 (dd, *J* = 0.9, 8.5 Hz, 1H), 7.97 - 7.92 (m, 1H), 7.63 (ddd, *J* = 8.4, 6.9, 1.3 Hz, 1H), 7.56 (d, *J* = 4.5 Hz, 1H), 7.35 (ddd, *J* = 8.4, 6.9, 1.3 Hz, 1H), 5.75 - 5.65 (m, 1H), 5.65 - 5.62 (m, 1H), 4.96 - 4.87 (m, 2H), 4.56 (br s, 1H), 3.51-3.42 (m, 1H), 3.11 - 3.00 (m, 2H), 2.66 - 2.54 (m, 2H), 2.28 - 2.20 (m, 1H), 1.82 - 1.69 (m, 3H), 1.55 - 1.42 (m, 2H).

The ^{1}H NMR results corresponded to those reported in literature. [56]

_N_-benzyl-_epi_-cinchonidinium bromide 24c

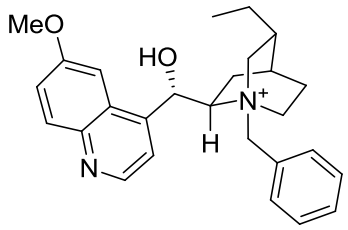


Following General Procedure I, *epi*-chinchonidine (0.40 g, 1.36 mmol) and benzyl bromide (0.16 ml, 1.36 mmol) gave the product as a white solid (reaction time 7 h). Isolated yield 93%.

^{1}H NMR ($CDCl_3$, 400 MHz) δ = 8.81 (d, *J* = 4.5 Hz, 1H), 8.18 - 8.12 (m, 1H), 7.82 (d, *J*=4.5 Hz, 1H), 7.70 - 7.60 (m, 3H), 7.25 - 7.10 (m, 5H), 6.60 - 6.56 (m, 1H), 6.56-6.50 (m, 1H), 5.95 (d, *J* = 11.9 Hz, 1H), 5.56 (d, *J* = 11.9 Hz, 1H), 5.46 - 5.35 (m, 1H), 5.33 - 5.26 (m, 1H), 4.91 (dd, *J* = 10.4, 1.3 Hz, 1H), 4.69 - 4.58 (m, 1H), 4.18 - 4.09 (m, 1H), 3.91 -3.83 (m, 1H), 3.16 – 3.06 (m, 2H), 2.47 (br s, 1H), 2.12 - 2.00 (m, 1H), 1.95 - 1.79 (m, 2H), 1.64 - 1.52 (m, 1H), 1.08 - 0.98 (m, 1H).

The ^{1}H NMR results for this compound have been reported in literature. [56]

_N_-benzyldehydroquinidinium bromide 162a



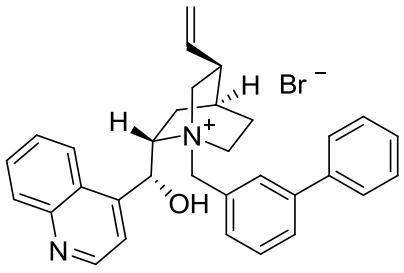
Following General Procedure I: hydroquinidine (0.20 g, 0.61 mmol) and 3-phenylbenzyl bromide (0.073 ml, 0.61 mmol) gave the product as a lilac solid (reaction time 7.5 h). Isolated yield 100%.

^{13}C NMR ($CDCl_3$, 400 MHz) δ ppm 158.0, 147.3, 144.1, 143.0, 134.0, 131.6, 130.3, 129.1, 127.3, 126.2, 120.9, 120.7, 102.6, 68.1, 66.0, 62.8, 56.8, 56.2, 55.9, 36.1, 24.6, 24.5, 24.3, 21.4, 11.5.

^{1}H NMR ($CDCl_3$, 400 MHz) δ ppm 9.56 (d, *J* = 4.5 Hz, 1H), 7.90 (d, *J* = 9.2 Hz, 1H), 7.74-7.69 (m, 3H), 7.42 (d, *J* =2.5, 1H), 7.39-7.28 (m, 3H), 7.20 (dd, *J* = 9.2, 2.6 Hz, 1H), 6.64-6.60 (m, 1H), 6.48-6.43 (m, 1H), 5.62 (d, *J* = 12.1 Hz, 1H), 5.09 (d, *J* = 12.0 Hz, 1H), 4.27-4.11 (m, 2H), 4.00-3.92 (m, 1H), 3.89(s, 3H), 3.42-3.31 (m, 1H), 2.90-2.78 (m, 1H), 2.47-2.38 (m, 1H), 2.38-2.28 (m, 1H), 1.82-1.67 (m, 2H), 1.66-1.45 (m, 4H), 0.98-0.89(m, 1H), 0.89-0.80 (m, 3H).

HRMS (Q-TOF): *m/z* calculated for $C_{27}H_{33}N_2O_2$ $[M]^+$ 417.2542, found: 417.2543.

_N_-(3-phenyl)benzylcinchonidinium bromide 163b



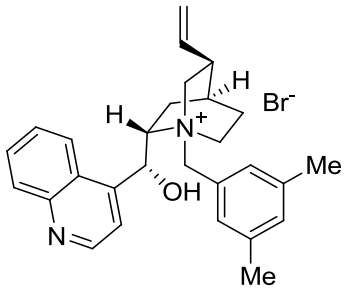
Following General Procedure II: cinchonidine (0.40 g, 1.36 mmol, 100 mol-%) and 3-phenylbenzyl bromide (0.37 g, 1.50 mmol, 110 mol-%) gave the product as a slightly peach coloured solid (reaction time 6h). Isolated yield 95%.

^{13}C NMR (DMSO, 400 MHz) δ ppm 150.2, 147.6, 145.2, 140.7, 139.3, 138.1, 132.7, 132.0, 129.8, 129.5, 129.4, 129.0, 128.7, 128.3, 127.9, 127.3, 126.9, 124.3, 123.7, 120.1, 116.4, 67.6, 64.0, 62.5, 59.3, 50.8, 36.9, 25.9, 24.3, 21.0.

^{1}H NMR (DMSO, 400 MHz) δ ppm 9.00 (d, *J* = 4.3 Hz, 1H), 8.37 (d, *J* = 8.3 Hz, 1H), 8.15-8.07 (m, 2H), 7.91-7.63 (m, 9H), 7.55-7.47 (m, 2H), 7.46-7.39 (m, 1H), 6.78 (d, *J* = 4.5 Hz, 1H), 6.64-6.58 (m, 1H), 5.70 (ddd, *J* = 17.0, 10.3, 6.4 Hz, 1H), 5.36-5.27 (m, 1H), 5.19 (d, *J* = 15.8 Hz, 2H), 4.95 (d, *J* = 10.5 Hz, 1H), 4.45-4.34 (m, 1H), 4.03-3.94 (m, 1H), 3.92-3.82 (m, 1H), 3.49-3.28 (m, 4H), 2.72 (brs, 1H), 2.20-1.97 (m, 3H), 1.91-1.76 (m, 1H), 1.40-1.28 (m, 1H).

HRMS (Q-TOF): *m/z* calculated for $C_{32}H_{33}N_2O$ $[M]^+$ 461.2593, found: 461.2608.

_N_-(3,5-dimethyl)benzylcinchonidinium bromide 164b



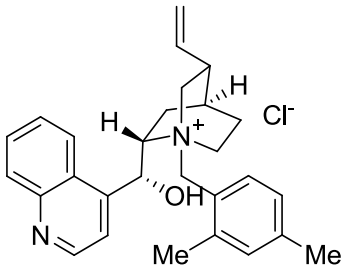
Following General Procedure I, cinchonidine (0.50 g, 1.70 mmol) and α-bromoesitylene (0.34 g, 1.70 mmol) gave the product as a white solid (reaction time 5h). Isolated yield 91%.

^{13}C NMR ($CDCl_3$, 400 MHz) δ ppm 149.6, 147.3, 144.7, 138.2, 136.2, 131.6, 131.6 129.6, 128.5, 127.4, 126.9, 123.8 123.2, 119.9, 117.8, 66.8, 65.2, 62.4, 60.2, 50.5, 38.0, 26.6, 25.2, 22.5, 21.3.

^{1}H NMR ($CDCl_3$, 400 MHz) δ ppm 8.80 (d, *J* = 4.5 Hz, 1H), 8.20-8.13 (m, 1H), 7.82 (d, *J* = 4.4 Hz, 1H), 7.69-7.63 (m, 1H), 7.31-7.26 (m, 2H), 7.22-7.14 (m, 2H), 7.82 (s, 1H), 6.62-6.57 (m, 1H), 6.52-6.56 (m, 1H), 5.90-5.83 (m, 1H), 5.47-5.36 (m, 2H), 5.33-5.25 (m, 1H), 4.90 (dd, *J* = 10.4, 1.2 Hz, 1H), 4.66-4.56 (m, 1H), 4.17-4.08 (m, 1H), 3.93-3.85 (m, 1H), 3.23-3.11 (m, 2H), 2.52-2.43 (m, 1H), 2.21 (s, 6H), 2.09-1.99 (m, 1H), 1.92-1.80 (m, 2H), 1.63-1.53 (m, 1H), 1.06-0.96 (m, 1H).

HRMS (Q-TOF): *m/z* calculated for $C_{28}H_{33}N_2O$ $[M]^+$ 413.2593, found: 413.2598.

_N_-(2,4-dimethyl)benzylcinchonidinium chloride 165b



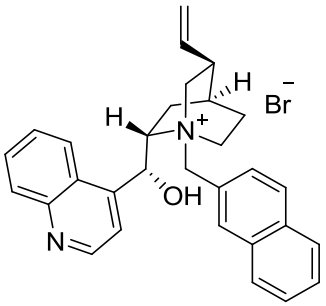
Following General Procedure I, cinchonidine (0.50 g, 1.70 mmol) and 2,4-dimethylbenzyl chloride (0.25 ml, 1.70 mmol) gave the product as a white solid (reaction time 25 h). Isolated yield 66%.

^{13}C NMR ($CDCl_3$, 400 MHz) δ ppm 149.3, 146.9, 145.5, 140.3, 139.7, 136.0, 135.3, 131.9 129.2, 128.2, 126.9, 126.6, 123.7 123.3, 123.2, 119.6, 117.7, 66.1, 65.9, 59.4, 58.8, 49.6, 38.0, 26.3, 25.4, 22.8, 21.3, 21.08.

^{1}H NMR ($CDCl_3$, 400 MHz) δ ppm 8.77 (d, *J* = 4.4 Hz, 1H), 8.29 (d, *J* = 8.3 Hz, 1H), 7.85-7.79 (m, 2H), 7.58 (d, *J* = 5.8 Hz, 1H), 7.53 (d, *J* = 7.7 Hz, 1H) 7.07-6.99 (m, 1H), 6.94-6.86 (m, 2H), 6.63 (s, 1H), 6.57-6.50 (m, 1H), 6.11 (d, *J* = 12.2 Hz, 1H), 5.50 (d, *J* = 12.3 Hz, 1H), 5.46-5.31 (m, 2H), 4.90-4.83 (m, 1H), 4.67-4.55 (m, 1H), 4.37-4.27 (m, 1H), 4.18-4.10 (m, 1H), 3.07 (dd, *J* = 12.6, 10.6 Hz, 1H) 2.87-2.77 (m, 1H), 2.47-2.38 (m, 1H), 2.32-2.27 (m, 6H), 2.03-1.93 (m, 1H), 1.84 (brs, 1H), 1.76-1.66 (m, 1H), 1.57-1.45 (m, 1H), 0.94-0.81 (m, 1H).

HRMS (Q-TOF): *m/z* calculated for $C_{28}H_{33}N_2O$ $[M]^+$ 413.2593, found: 413.2603.

_N_-(2-naphtylmethyl)cinchonidinium bromide 166b

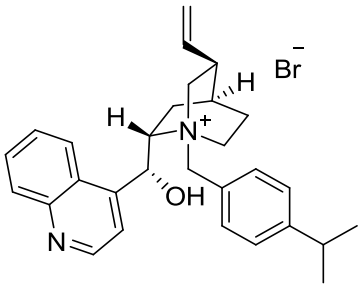


Following General Procedure I: cinchonidine (0.40 g, 1.36 mmol) and 2-(bromomethyl)naphthalene (0.30 g, 1.36 mmol) gave the product as a slightly peach colored solid (reaction time 5 h). Isolated yield 92%.

1H NMR ($CDCl_3$, 400 MHz) δ ppm 8.78 (d, *J* = 4.5 Hz, 1H), 8.19 - 8.10 (m, 1H), 7.77 (d, *J* = 4.5 Hz, 1H), 7.64 - 7.47 (m, 2H), 7.10 - 7.01 (m, 1H), 7.01 - 6.96 (m, 2H), 6.48 - 6.42 (m, 1H), 6.42 - 6.37 (m, 1H), 6.23 (d, *J* = 12.2 Hz, 1H), 5.61 (d, *J* = 12.1 Hz, 1H), 5.45 - 5.31 (m, 1H), 4.96 - 4.84 (m, 1H), 4.67 - 4.56 (m, 1H), 4.28 - 4.17 (m, 1H), 4.08 - 3.98 (m, 1H), 3.13 - 2.99 (m, 2H), 2.57 - 2.47 (m, 1H), 2.18 - 2.02 (m, 1H), 1.95 (br s, 1H), 1.92 - 1.77 (m, 1H), 1.73 - 1.56 (m, 1H), 1.06 - 0.93 (m, 1H)

^{1}H NMR results for this compound have been reported in literature. [56]

_N_-(4-isopropyl)benzylcinchonidinium bromide 167b



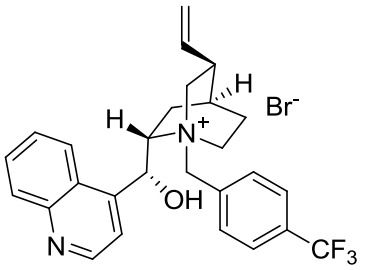
Following General Procedure I, cinchonidine (0.50 g, 1.70 mmol) and 4-isopropyl benzyl bromide (0.30 mL, 1.76 mmol) gave the product as a pinkish solid (reaction time 4 h). Isolated yield 89%.

^{13}C NMR ($CDCl_3$, 400 MHz) δ ppm 150.9, 149.8, 147.5, 144.7, 136.3, 134.1, 129.9, 128.7, 127.5, 126.9, 124.4, 124.0, 123.2, 120.1, 117.9, 67.5, 64.8, 62.5, 60.4, 50.7, 38.0, 33.8, 26.6, 25.1, 24.2, 23.5, 22.2.

^{1}H NMR ($CDCl_3$, 400 MHz) δ ppm 8.82 (d, *J* = 4.5 Hz, 1H), 8.16-8.10 (m, 1H), 7.81 (d, *J* = 4.5 Hz, 1H), 7.79-7.74 (m, 1H), 7.68 (d, *J* = 8.1 Hz, 2H), 7.33-7.25 (m, 2H), 7.07 (d, J = 8.0 Hz, 2H), 6.60-6.52 (m, 2H), 5.73 (d, *J* = 12.0, 1H), 5.51 (d, *J* = 12.0 Hz, 1H), 5.43 (ddd, *J* = 17.1, 10.5, 6.3 Hz, 1H), 5.25-5.17 (m, 1H), 4.91 (dd, *J* = 10.5, 1.2 Hz, 1H) 4.67-4.57 (m, 1H), 4.08-4.00 (m, 1H), 3.81-3.72 (m, 1H), 3.27-3.11 (m, 2H), 2.81 (dddd, app. nonet, *J* = 6.9 Hz, 1H), 2.50 (brs, 1H), 2.14-2.05 (m, 1H), 1.98-1.88 (m, 2H), 1.67-1.56 (m, 1H), 1.24 (dd, *J* = 13.3 Hz, 6.9, 6H), 1.15-1.04 (m, 1H).

HRMS (Q-TOF): *m/z* calculated for $C_{29}H_{35}N_2O$ $[M]^+$ 427.2749, found: 427.2741.

_N_-(4-trifluoromethylbenzyl)cinchonidinium bromide 22b



Following General Procedure I, cinchonidine (0.40 g, 1.36 mmol) and 4-(trifluoromethyl)benzyl bromide (0.21 mL, 1.36 mmol) gave the product as a white solid (reaction time 4 h). Isolated yield 90%.

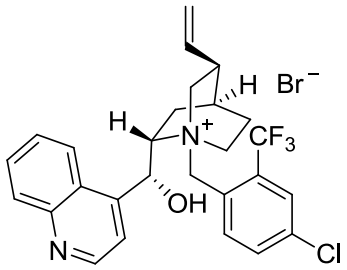
^{13}C NMR ($CDCl_3$, 400 MHz) δ ppm 149.5, 147.1, 144.1, 135.7, 134.6, [132.8, 132.4, 132.1, 131.8], 131.2, 129.7, 128.4, [127.5, 124.8, 122.1, 119.4], 127.3, [125.5, 125.4], 123.3, 122.7, 119.7, 118.1, 67.2, 65.3, 60.9, 60.1, 50.6, 37.8, 26.3, 25.1, 22.6.

^{1}H NMR ($CDCl_3$, 400 MHz) δ ppm 8.79 (d, *J* = 4.5 Hz, 1H), 8.19-8.14 (m, 1H), 7.88 (d, *J* = 7.8 Hz, 2H), 7.79 (d, *J* = 4.4 Hz, 1H), 7.56-7.51 (m, 1H), 7.41 (d, *J* = 8.0 Hz, 2H), 7.04-6.99 (m, 2H), 6.54 (d, *J* = 5.88 Hz, 1H), 6.50-6.46 (m, 1H), 6.36 (d, *J* = 11.9 Hz, 1H), 5.55 (d, *J* = 11.9 Hz, 1H), 5.43-5.29 (m, 2H), 4.93-4.89 (m, 1H), 4.69-4.59 (m, 1H), 4.27-4.19 (m, 1H), 4.04-3.97 (m, 1H), 3.07-2.90 (m, 2H), 2.52-2.45 (m, 1H), 2.12-2.02 (m, 1H), 1.93 (brs, 1H), 1.88-1.79 (m, 1H), 1.66-1.55 (m, 1H), 1.04-0.94 (m, 1H).

Note: N-(4-trifluoromethylbenzyl)cinchonidinium bromide is a well-known and used compound, but no NMR data could be found [40].

HRMS (Q-TOF): *m/z* calculated for $C_{27}H_{28}F_3N_2O$ $[M]^+$ 453.2161, found: 453.2154.

***N*-(4-chloro-[2-trifluoromethyl])benzylcinchonidinium bromide 168b**



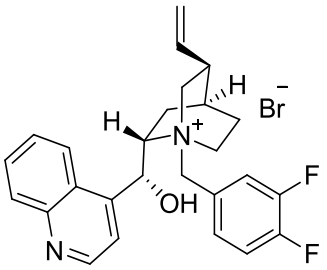
Following General Procedure II: cinchonidine (0.40 g, 1.36 mmol, 100 mol-%) and 4-chloro-2-(trifluoromethyl)benzyl bromide (0.407 g, 1.49 mmol, 110 mol-%) gave the product as a white solid (reaction time 7h). Isolated yield 88%.

^{13}C NMR ($CDCl_3$, 400 MHz) δ ppm 150.2, 147.9, 144.5, 138.5, 137.9, 135.7, 133.2, [133.1, 132.8, 132.5, 132.2], 130.7, 129.2, [128.3, 128.3, 128.2, 128.2], 127.5, [127.4, 124.6, 121.9, 119.2], 124.3, 123.7, 122.3, 120.3, 118.3, 71.5, 64.0, 61.2, 59.1, 52.1, 38.0, 26.1, 25.1, 21.9.

^{1}H NMR ($CDCl_3$, 400 MHz) δ ppm 8.93 (d, *J* = 4.5 Hz, 1H), 8.44 (d, *J* = 8.4Hz, 1H), 8.09 (d, *J* = 8.3 Hz, 1H), 8.03 (d, *J* = 7.84 Hz, 1H), 7.87 (d, *J* = 4.4 Hz, 1H), 7.74 (d, *J* = 2.2 Hz, 1H), 7.68 (dd, *J* = 8.4, *J* = 2.1, 1H), 7.54 (dt, *J* = 44.5, 7.4 Hz, 2H), 6.78 (d, *J* = 6.1 Hz, 1H), 6.54-6.44 (m, 1H), 6.38 (d, *J* = 6.4 Hz, 1H), 5.52 (ddd, *J* = 17.0, 10.5, 6.4 Hz, 1H), 5.36-5.24 (m, 1H), 5.17-5.08 (m, 2H), 5.01 (dd, *J* = 10.6, 1.2 Hz, 1H), 3.96-3.86 (m, 1H), 3.46 (br, 1H), 3.25 (td, *J* = 11.5, 5.6Hz, 1H), 3.08 (dd, *J* = 12.5, 10.5 Hz, 1H), 2.64-2.55 (m, 1H), 2.40-2.29 (m, 1H), 2.05-1.99 (m, 1H), 1.87-1.76 (m, 1H, partially beneath THF), 1.37-1.26 (m, 1H).

HRMS (Q-TOF): *m/z* calculated for $C_{27}H_{27}ClF_3N_2O$ $[M]^+$ 487.1764, found: 487.1774.

_N_-(3,4-difluorobenzyl)cinchonidinium bromide 169b



Following General Procedure I, cinchonidine (0.50 g, 1.70 mmol) and 3,4-difluorobenzyl bromide (0.22 mL, 1.70 mmol) gave the product as a beige solid (reaction time 5 h). Isolated yield 90%.

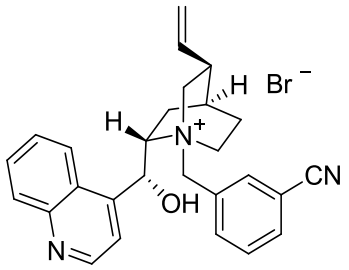
^{13}C NMR ($CDCl_3$, 400 MHz) δ ppm [152.8, 152.7, 151.1, 150.9], [150.3, 150.2, 148.6, 148.4] 149.4, 147.0, 144.1, 135.7, [131.2, 131.1, 131.1, 131.1] 129.6, 128.3, 127.2, [124.3, 124.2, 124.2], 123.3, [123.3, 123.1] 122.7, 119.6, 118.0, [117.7, 117.5], 66.8, 65.3, 60.5, 59.8, 50.3, 37.8, 26.3, 25.2, 22.7.

^{1}H NMR ($CDCl_3$, 400 MHz) δ ppm 8.78 (d, *J* = 4.5 Hz, 1H), 8.17-8.11 (m, 1H), 7.77 (d, *J* = 4.4 Hz, 1H), 7.65-7.48 (m, 3H), 7.10-7.01 (m, 1H), 7.01-6.95 (m, 2H), 6.49-6.6.41 (m, 1H), 6.42-6.37 (m, 1H), 6.23 (d, *J* = 12.1 Hz, 1H), 5.61 (d, *J* = 12.1 Hz, 1H), 5.45-5.31 (m, 2H), 4.94-4.87 (m, 1H), 4.68-4.56 (m, 1H), 4.26-4.17 (m, 1H), 4.07-3.99 (m, 1H), 3.13-2.99 (m, 2H), 2.56-2.47 (m, 1H), 2.16-2-03 (m, 1H), 1.95 (brs, 1H), 1.88-1.77 (m, 1H), 1.70-1.58 (m, 1H), 1.04-0.93 (m, 1H).

Note: N-(4-trifluoromethylbenzyl)cinchonidinium bromide is a well-known and used compound, but no NMR data could be found [19].

HRMS (Q-TOF): *m/z* calculated for $C_{26}H_{27}F_2N_2O$ $[M]^+$ 421.2091, found: 421.2100.

_N_-(3-cyano)benzylcinchonidinium bromide 170b



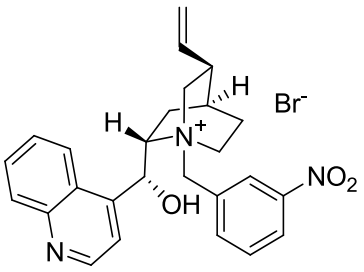
Following General Procedure II: cinchonidine (0.40 g, 1.36 mmol, 100 mol-%) and 3-cyanobenzyl bromide (0.29 g, 1.49 mmol, 110 mol-%) gave the product as a white solid (reaction time 6h). Isolated yield 92%.

^{13}C NMR (DMSO, 400 MHz) δ ppm 150.1, 147.6, 145.1, 138.6, 138.0, 137.2, 133.7, 130.1, 129.8, 129.6, 129.4, 127.3, 124.2, 123.7, 120.1, 118.4, 116.4, 112.0, 67.8, 64.0, 61.3, 59.2, 50.7, 36.8, 25.8, 24.2, 21.0.

^{1}H NMR (DMSO, 400 MHz) δ ppm 8.99 (d, *J* = 4.3 Hz, 1H), 8.37-8.32 (m, 2H), 8.17 (d, *J* = 7.6 Hz, 1H), 8.09 (dd, *J* = 14.9, 8.0 Hz, 2H), 7.88-7.72 (m, 4H), 6.81-6.71 (m, 1H), 6.57-6.53 (m, 1H), 5.68 (ddd*, J* = 17.0, 10.5, 6.2 Hz, 1H), 5.36-5.17 (m, 3H), 4.95 (d*, J* = 10.5 Hz, 1H), 4.41-4.30 (m, 1H), 4.00-3.92 (m, 1H), 3.92-3.83 (m, 1H), 3.37 (s, 2H), 3.33-3.21 (m, 1H), 2.67 (brs, 1H), 2.17-1.97 (m, 2H), 1.87-1.75 (m, 1H), 1.33-1.22 (m, 1H).

HRMS (Q-TOF): *m/z* calculated for $C_{27}H_{28}N_3O$ $[M]^+$ 410.2232, found: 410.2254.

_N_-(3-nitro)benzylcinchonidinium bromide 171b



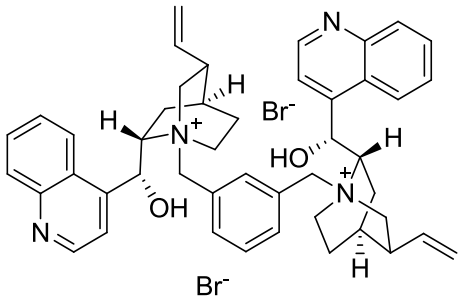
Following General Procedure I: cinchonidine (0.5 g, 1.70 mmol) and 3-phenylbenzyl bromide (0.37 g, 1.70 mmol) gave the product as a slightly beige solid (reaction time 10 h). Isolated yield 94%.

^{13}C NMR (DMSO, 400 MHz) δ ppm 150.2, 148.0, 147.6, 145.1, 140.3, 138.0, 130.5, 130.0, 129.8, 129.4, 128.5, 127.3, 124.9, 124.2, 123.7, 120.1, 116.4, 67.9, 64.0, 61.2, 59.1, 50.6, 36.9, 25.8, 24.2, 21.0.

^{1}H NMR (DMSO, 400 MHz) δ ppm 9.00 (d, *J* = 4.3 Hz, 1H), 8.72 (s, 1H), 8.43 (d, *J* = 7.8 Hz, 1H), 8.36 (d, *J* = 8.2 Hz, 1H), 8.28 (d, *J* = 7.4 Hz, 1H), 8.12 (d, *J* = 8.3 Hz, 1H), 7.93-7.74 (m, 4H), 6.81-6.76 (m, 1H), 6.63-6.55 (m, 1H), 5.68 (ddd, *J* = 17.0, 10.4, 6.4 Hz, 1H), 5.45 (d, J = 12.2 Hz, 1H), 5.33 (d, *J* = 12.2 Hz, 1H), 5.24-5.15 (m, 1H), 4.96 (d, *J* = 10.6 Hz, 1H), 4.44-4.34 (m, 1H), 4.02-3.86 (m, 2H), 3.40-3.24 (m, 2H), 2.70-2.60 (m, 1H), 2.19-1.97 (m, 3H), 1.86-1.73 (m, 1H) 1.35-1.24 (m, 1H).

HRMS (Q-TOF): *m/z* calculated for $C_{26}H_{28}N_3O_3$ $[M]^+$ 430.2131, found: 430.2131.

1,3-Bis(cinchonidinium-*N*-methyl)benzyl dibromide 172



To a flask equipped with a magnetic stirring bar and a reflux condenser was added cinchonidine, (1.00 g, 3.39 mmol, 200 mol-%), dry THF (34 ml (0.1 M)), and 1,3-bis(bromomethyl)-benzene (0.448 g, 1.70 mmol, 100 mol-%). The mixture was heated to reflux until judged to be complete by LC-MS-analysis (10h). The mixture was then cooled to room temperature and MTBE was added (70 ml). The resulting suspension was stirred for 1h at room temperature and the precipitated solids were isolated by filtration, yielding the product as a beige solid in a 98% yield.

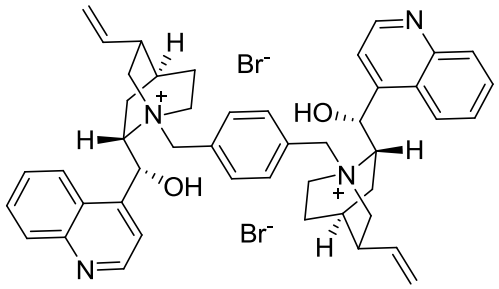
^{13}C NMR (DMSO, 400 MHz) δ ppm 150.1, 147.6, 145.1, 138.9, 138.1, 135.3, 129.6, 128.6, 127.4, 124.2, 123.7, 120.2, 116.2, 67.6, 64.2, 62.1, 59.1, 50.5, 36.7, 36.7, 25.8, 24.1, 21.1.

^{1}H NMR (DMSO, 400 MHz) δ ppm 9.01 (d, *J* = 4.2 Hz, 2H), 8.39 (d, *J* = 8.2 Hz, 2H), 8.18 (s, 1H), 8.12 (d, *J* = 8.3 Hz, 2H), 7.99 (d, *J* = 7.4 Hz, 2H), 7.90-7.73 (m, 7H), 6.82-6.76 (m, 2H), 6.64-6.58 (m, 2H), 5.69 (ddd, *J* = 16.9, 10.3, 6.3 Hz, 2H), 5.39-

5.16 (m, 6H), 4.96 (d, *J* = 10,4 Hz, 2H), 4.39-4.27 (m, 2H), 4.06-3.78 (m, 4H), 3.69-3.55 (m, 2H), 2.78 (m, 2H), 2.19-1.79 (m, 10H), 1.37-1.21 (m, 2H).

HRMS (Q-TOF): *m/z* calculated for $C_{46}H_{51}N_4O_2$ $[M-H]^+$ 691.4012, found: 691.3931.

1,4-Bis(cinchonidinium-*N*-methyl)benzyl dibromide 173



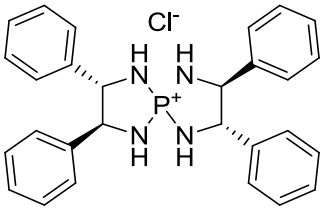
To a flask equipped with a magnetic stirring bar and a reflux condenser was added cinchonidine, (1.00 g, 3.39 mmol, 200 mol-%), dry THF (34 ml, 0.1 M), and 1,3-bis(bromomethyl)-benzene (0.448 g, 1.70 mmol, 100 mol-%). The mixture was heated to reflux until the reaction did not seem to precede further (5.5h). The mixture was then cooled to room temperature and MTBE was added (70 ml). The resulting suspension was stirred for at least 1h and the precipitated solids were isolated by filtration. The crude product was purified by flash column chromatography (0-20% MeOH in CH_2Cl_2 used as eluent, fractions containing product at approximately 15%). The fractions containing the product were combined yielding the product as a peach colored solid in a 46% yield.

^{13}C NMR (DMSO, 400 MHz) δ ppm 150.2, 147.6, 145.3, 138.3, 134.1, 129.9, 129.8, 129.5, 127.3, 124.3, 123.7, 120.1, 116.2, 67.6, 64.2, 62.1, 59.1, 50.5, 36.6, 25.9, 24.1, 21.2.

^1H NMR (DMSO, 400 MHz) δ ppm 9.00 (d, *J* = 4.5 Hz, 2H), 8.37 (d, *J* = 8.4 Hz, 2H), 8.12 (dd, *J* = 8.4, 1.1 Hz, 2H), 7.93 (s, 4H), 7.90-7.82 (m, 4H), 7.81-7.75 (m, 2H), 6.78-6.74 (m, 2H), 6.63-6.55 (m, 2H), 5.68 (ddd, *J* = 17.1, 10.6, 6.3 Hz, 2H), 5.31-5.15 (m, 6H), 4.95 (d, *J* = 10.6 Hz, 2H), 4.33-4.21 (m, 2H), 4.00-3.91 (m, 2H), 3.87-3.75 (m, 4H), 3.59-3.49 (m, 2H),2.89-2.80 (m, 2H), 2.16-2.06 (m, 2H), 2.04-1.92 (m, 6H), 1.32-1.21 (m, 2H).

HRMS (Q-TOF): *m/z* calculated for $C_{46}H_{51}N_4O_2$ $[M-H]^+$ 691.4012, found: 691.3940.

Chiral tetraaminophosphonium chloride 174



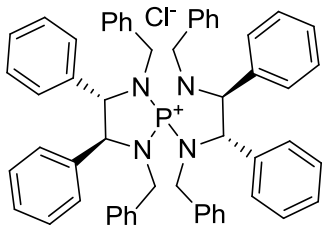
Chiral tetraaminophosphonium chloride **174** was prepared according to the procedure reported by Ooi and co-workers. [30]

The chiral tetraaminophosphonium chloride **174** was prepared by dissolving (1*S*,2*S*)-(-)-1,2-diamino-1,2-diphenylethane (0.500 g, 2.353 mmol, 200 mol-%) in dichloromethane (6 ml, 0.4 M). Phosphorus pentachloride (0.245 g, 1.177 mmol, 100 mol-%) was added to the reaction mixture portion wise. The mixture was placed under a nitrogen atmosphere before the addition of pyridine (1.9 ml, 24.1 mmol, 20.5 eq). The reaction mixture was stirred for 2h before the addition of triethylamine (1.6 ml, 11.8 ml, 10 eq). The reaction mixture was stirred for another 3h before all volatiles were evaporated from the reaction mixture. The remainder was triturated with 1M aqueous hydrochloric acid solution (5.5 ml) and the remaining solids were washed with methyl *tert*-butyl ether. The crude product was purified by flash column chromatography using methanol and dichloromethane (0-20%) as eluent. The chiral tetraminophosphonium chloride **174** was obtained as a solid (0.205 g, 36%).

^{1}H NMR (CD_3OD, 400 MHz) δ ppm 7.41 - 7.29 (m, 20H), 4.54 (d, J = 3.3 Hz, 4H).

The ^{1}H NMR results corresponded to those reported in literature. [30]

Chiral tetraaminophosphonium chloride 65a



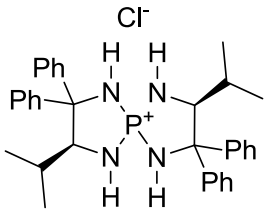
Chiral tetraaminophosphonium chloride **65a** was prepared according to the procedure reported by Ooi and co-workers with some minor variations [30]

Chiral tetraaminophosphonium chloride **65a** was prepared by dissolving the chiral tetraaminophosphonium chloride **174** (0.180 g, 0.370 mmol, 1 eq) obtained from the reaction above in dry *N,N*-dimethyl formamide (7.4 ml, 0.05 M). To this solution benzyl bromide (0.44 ml, 3.7 mmol, 10 eq) was added. A suspension of sodium hydride (0.089 g, 3.70 mmol, 10 eq) and acetonitrile (3.7 ml, 1 M) was created by cooling the acetonitrile to 0 ºC and adding the sodium hydride to it in portions. The mixture was kept on the ice bath and put under a nitrogen atmosphere. The mixture containing the chiral tetraaminophosphonium chloride **174** was added to the sodium hydride suspension drop wise. The mixture was stirred at room temperature overnight. The reaction was monitored using UPLC-MS analysis, and when no starting material could be detected, the reaction mixture was cooled to 0 ºC using an ice bath, before adding ethanol (8 ml) drop wise to the mixture. The mixture was stirred in the ice bath for an hour. Volatiles were evaporated and the remainder was diluted with dichloromethane and washed with 1 M aqueous hydrochloric acid solution. The organic phase was dried over sodium sulfate and solvents were evaporated. The crude product was purified by flash column chromatography using methanol and dichloromethane (0-20%). A white powder (0.159 g, 51%) was obtained.

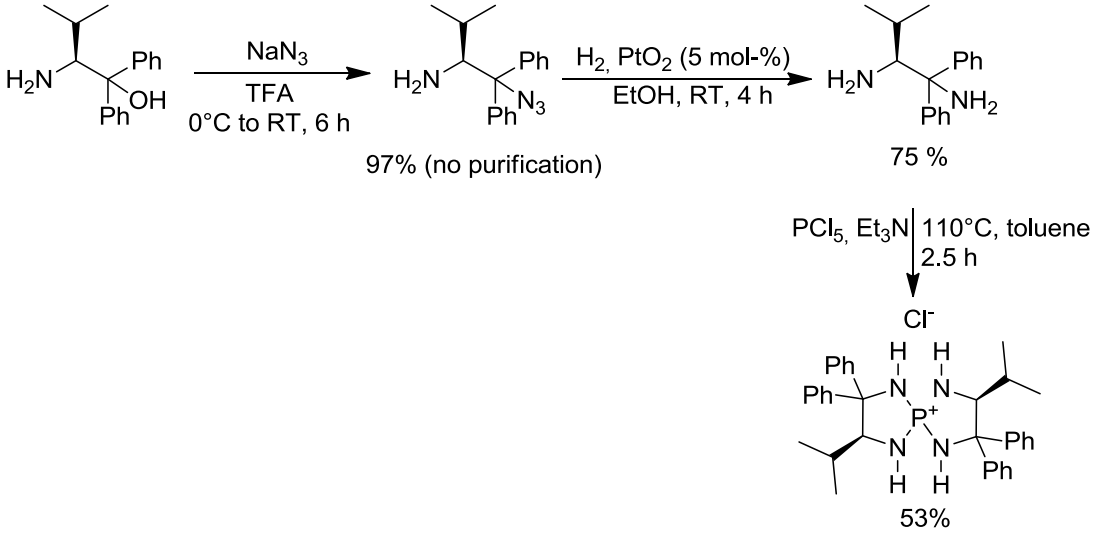
^{1}H NMR ($CDCl_3$, 400 MHz) δ ppm 7.39 - 7.28 (m, 16H), 7.26 - 7.21 (m, 8H), 7.13 - 7.07 (m, 8H), 6.95 - 6.90 (d, *J* = 7.5 Hz, 8H), 4.78 (s, 4H), 4.26 (dd, *J* = 15.3, 12.8 Hz, 4H), 3.94 (t, *J* = 15.2 Hz, 4H).

The ^{1}H NMR results corresponded to those reported in literature. [30]

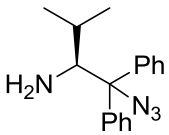
Chiral tetraaminophosphonium chloride 45a



Chiral tetraaminophosphonium chloride **45a** was prepared according to the procedure reported by Ooi and co-workers [26] with some minor variations (Scheme 68). The first variation was that the (*S*)-2-amino-3-methyl-1,1-diphenylbutan-1-ol was not made into a hydrochloric acid before aziridination. The second change was that platinum (IV) oxide was used instead of palladium. This was done because in the first batch the UPLC-MS analysis results indicated a broad spectrum of products, probably over-hydrogenated products.

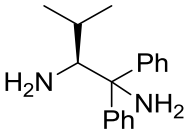


Scheme 68. Chiral tetraaminophosphonium chloride preparation.



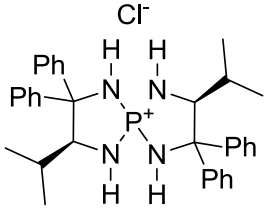
(*S*)-1-azido-3-methyl-1,1-diphenylbutan-2-amine was prepared by cooling trifluoroacetic acid (10 ml, 0.2 M) to 0ºC, before adding sodium azide (0.636 g, 9.79 mmol, 100 mol-%) in a portion wise manner to a 50 ml round-bottomed flask. (*S*)-2-amino-3-methyl-1,1-diphenyl-1-butanol (0.500 g, 1.958 mmol, 500 mol-%) was added

to the solution in a portion wise manner. The reaction mixture was stirred for 6h at room temperature before it was poured onto crushed ice. The resulting mixture was stirred vigorously. Sodium hydroxide pellets were added to the mixture until a pH of 11-12 was achieved. The resulting mixture was extracted with ethyl acetate (3 x 50 ml) and the combined organic phases were washed with brine (2 x 50 ml) and dried over sodium sulfate. The solvents were evaporated yielding colorless oil (0.549 g, 97%). The product was used for the next step without purification.



(*S*)-3-methyl-1,1-diphenylbutan-1,2-diamine was prepared by adding the (*S*)-1-azido-3-methyl-1,1-diphenylbutan-2-amine (0.549 g, 1.712 mmol, 100 mol-%) obtained from the previous reaction to ethanol (8.6 ml, 0.2 M) in a 50 ml round-bottomed flask. Platinum-(IV)oxide (0.019 g, 0.086 mmol, 5 mol-%) was added to the mixture and the atmosphere was replaced with hydrogen. The reaction mixture was stirred at room temperature. The reaction was monitored by UPLC-MS analysis, and when judged to be complete, approximately 4h after initiation, the hydrogenation was terminated and active charcoal (0.076 g) was added to the mixture. The resulting mixture was stirred for 15 minutes before being filtered through a pad of Celite®. The solvents were evaporated from the filtrate yielding the crude product as a yellow liquid with white solids. The crude product was purified by flash column chromatography using a large silica column (24 g) and as eluents methanol and ethyl acetate (0-10%) were used. The product isolated was a white solid (0.326 g, 75%).

^{1}H NMR ($CDCl_3$, 400 MHz, δ ppm 7.51 - 7.42 (m, 4H), 7.32 - 7.25 (m, 4H), 7.22 - 7.15 (m, 2H), 3.67 (d, *J* = 1.8 Hz, 1H), 1.93 - 1.79 (m, 1H), 0.99 (d, *J* = 6.9 Hz, 3H), 0.75 (d, *J* = 6.7 Hz, 3H).



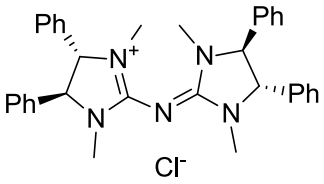
Chiral tetraaminophosphonium chloride **45a** was prepared by dissolving phosphorus pentachloride (0.147 g, 0.706 mmol, 100 mol-%) in toluene (3.5 ml, 0.2M). The (*S*)-3-

methyl-1,1-diphenylbutan-1,2-diamine (0.326 g, 1.412 mmol, 200 mol-%) was dissolved in a separate round-bottomed flask in toluene (3.5 ml, 0.4 M) and triethylamine (0.49 ml, 3.53 mmol, 500 mol-%). The phosphorus pentachloride solution was added to the (*S*)-3-methyl-1,1-diphenylbutan-1,2-diamine mixture. The mixture monitored by UPLC-MS analysis under the refluxation and when judged to be complete, after approximately 2 h, the heating was seized. The solvent in the reaction mixture was evaporated, and the remainder was dissolved in dichloromethane (20 ml) and was washed with 1M aqueous hydrochloric acid solution (30 ml). The organic phase was dried over sodium sulfate and solvents were evaporated. The crude product was purified by flash column chromatography using methanol and dichloromethane (0-10%) as eluents. The product attained was a yellow solid (0.212 g, 53%).

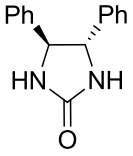
^{1}H NMR ($CDCl_3$, 400 MHz) δ ppm 7.36 - 7.28 (m, 14H), 7.24 - 7.17 (m, 6H), 4.83 (br s, 1H), 4.79 (br s, 1H), 1.67 - 1.55 (m, 2H), 0.91 (d, *J*=6.5 Hz, 6H), 0.78 (d, *J*=6.7 Hz, 6H).

The ^{1}H NMR results have been reported in literature. [26]

Pentanidium chloride 175

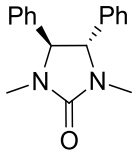


Chiral pentanidium chloride **175** was prepared according to the procedure reported by Tan and co-workers [50] with some minor variations.



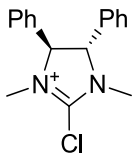
Step 1: (4*S*, 5*S*)-(-)-4,5-diphenylimidazolidin-2-one was prepared by dissolving (1*S*, 2*S*)-(-)-1,2-diphenylethane (2.123 g, 10 mmol, 100 mol-%) and triethylamine (4.18 ml, 30.0 mmol, 300 mol-%) in dry dichloromethane (25 ml, 0.4 M). The mixture was put under a nitrogen atmosphere and cooled to 0 ºC using an ice bath. Bis(trichloromethyl)carbonate (0.979 g, 3.30 mmol, 33 mol-%) was dissolved in dry

dichloromethane (5 ml, 0.66 M) and added to the mixture containing (1*S*, 2*S*)-(-)-1,2-diphenylethane in a drop wise manner. The reaction was monitored using UPLC-MS analysis and when judged to be complete, approximately 4 h after initiation of reaction, the reaction was quenched with distilled water (20 ml). Phases were separated and the aqueous phase was extracted with dichloromethane (3 x 30 ml). The combined organic phases were washed with brine (80 ml) and dried over sodium sulfate. Solvents were evaporated and the yellow solid obtained (2.38 g, 100%) was used for the next step without further purification.

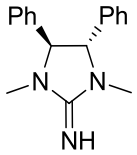


Step 2: (4*S*,5*S*)-1,3-dimethyl-4,5-diphenylimidazolidin-2-one was prepared by creating a suspension of sodium hydride (0.720 g, 30.0 mmol, 3 eq) and dry tetrahydrofuran (15 ml, 2 M). The suspension was put under a nitrogen atmosphere and cooled in an ice bath. To this suspension, (4*S*,5*S*)-(-)-4,5-diphenylimidazolidin-2-one (2.383 g, 10.00 mmol, 1 eq) dissolved in dry tetrahydrofuran (20 ml, 0.5 M) was added in a drop wise manner. The reaction mixture was stirred at room temperature for 15 minutes before being cooled to 0 ºC again. Iodomethane (2.3 ml, 37.0 mmol, 3.7 eq) was added to the reaction mixture. The reaction mixture was monitored by UPLC-MS analysis and was stirred at room temperature until judged to be complete, approximately 3 h. The reaction mixture was filtered through a pad of Celite® and the pad was washed with a generous amount of tetrahydrofuran. Solvents were evaporated from the filtrate and the crude product was purified by flash column chromatography using ethyl acetate and heptane (0-100%) as eluents. The ((4*S*,5*S*)-1,3-dimethyl-4,5-phenylimidazolidin-2-one was obtained as a yellowish solid (0.76 g, 29%).

^{1}H NMR ($CDCl_3$, 400 MHz) δ ppm 7.38 - 7.31 (m, 6H), 7.17 - 7.12 (m, 4H), 4.08 (s, 2H), 2.70 (s, 6H).

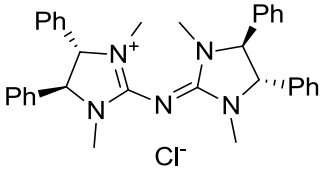


Step 3: (4*S*,5*S*)-2-chloro-1,3-dimethyl-4,5-diphenyl-4,5.dihydro-1H-imidazol-3-ium was obtained by dissolving the (4*S*,5*S*)-1,3-dimethyl-4,5-phenylimidazolidin-2-one (0.76 g, 2.58 mmol, 1 eq) obtained in the previous step (step 2) in dry toluene (20 ml, 0.13 M) under a nitrogen atmosphere. Oxalyl chloride (2.4 ml, 28.5 mmol, 10 eq) was added to the solution. The reaction mixture was refluxed overnight under a continuous nitrogen flow. The majority of the solvent had evaporated under night, so methyl *tert*-butyl ether (20 ml) and toluene (2 ml) was added to the round-bottomed flask in the morning and the resulting mixture was stirred at room temperature for 3 h before being filtered under a nitrogen flow. The product was obtained as a gray brown solid (0.538 g, 66%).



Step 4: (4*S*,5*S*)-1,3-dimethyl-4,5-diphenylimidazoline-2-imine was prepared by dissolving half of the (4*S*,5*S*)-2-chloro-1,3-dimethyl-4,5-diphenyl-4,5.dihydro-1H-imidazol-3-ium obtained in the previous step (step 3) in 2 M ammonia solution in methanol and poured into a round-bottomed pressure flask. The flask was put under a nitrogen atmosphere and sealed. The reaction mixture was heated to 60 ºC. The reaction mixture was heated overnight (approximately 19 h) and was cooled to room temperature in the morning. The pressure was released, and 40 ml of distilled water was added to the reaction mixture. The phases were separated and the aqueous phase was extracted with dichloromethane (3 x 20 ml). The combined organic phases were dried over sodium sulfate and solvents were evaporated yielding a brown crystalline solid (0.20 g, 80%).

^{1}H NMR ($CDCl_3$, 400 MHz) δ ppm 7.39 - 7.31 (m, 6H), 7.17 - 7.12 (m, 4H), 4.08 (s, 2H), 2.71 (s, 6H).



Step 5: Chiral pentanidium chloride **175** was prepared by adding the remainder of (4*S*,5*S*)-2-chloro-1,3-dimethyl-4,5-diphenyl-4,5.dihydro-1H-imidazol-3-ium (0.269 g,

0.942 mmol, 100 mol-%) and triethylamine (0.14 ml, 1.00 mmol, 106 mol-%) to dry acetonitrile (15 ml, 0.06 M). To this mixture the (4*S*,5*S*)-1,3-dimethyl-4,5-diphenylimidazoline-2-imine (0.20 g, 0.754 mmol, 80 mol-%) dissolved in dry acetonitrile (3 ml, 0.25 M) was added. The reaction mixture was stirred overnight. When judged to be complete, the reaction mixture was quenched with water (20 ml) and the resulting phases were separated. The aqueous phase was extracted using dichloromethane (3 x 20 ml). The combined organic phases were dried over sodium sulfate and solvents were evaporated. The crude product was purified by flash column chromatography using methanol and dichloromethane (0-20%) as eluents. Chiral pentanidium chloride **175** was obtained as a white solid (0.0236 g, 4.6%).

^{1}H NMR ($CDCl_3$, 400MHz) δ ppm 7.43 - 7.34 (m, 12H), 7.29 - 7.25 (m, 8H), 4.72 (s, 4H), 2.98 (s, 12H).

The ^{1}H NMR results corresponded to those reported in literature. [50]

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7. Appendices

Appendix 1: Methyl 4-cyano-2-methyl-2-phenylbutanoate **159**

Appendix 2: Ethyl 4-cyano-4-phenylvalerate **177**

Appendix 3: Diethyl 2-phenylpentanedioate **181**

Appendix 4: *N*-benzyldehydroquinidinium bromide **162a**

Appendix 5: *N*-(3-phenyl)benzylcinchonidinium bromide **163b**

Appendix 6: *N*-(3,5-methyl)benzylcinchonidinium bromide **164b**

Appendix 7: *N*-(2,4-methyl)benzylcinchonidinium chloride **165b**

Appendix 8: *N*-(4-isopropyl)benzylcinchonidinium bromide **167b**

Appendix 9: *N*-(trifluoromethyl)benzylcinchonidium bromide **22b**

Appendix 10: *N*-(4-chloro-[2-trifluoromethyl])benzylcinchonidinium bromide **168b**

Appendix 11: *N*-(3,4-difluoro)benzylcinchonidinium bromide **169b**

Appendix 12: *N*-(3-cyano)benzylcinchonidinium bromide **170b**

Appendix 13: *N*-(3-nitro)benzylcinchonidinium bromide **171b**

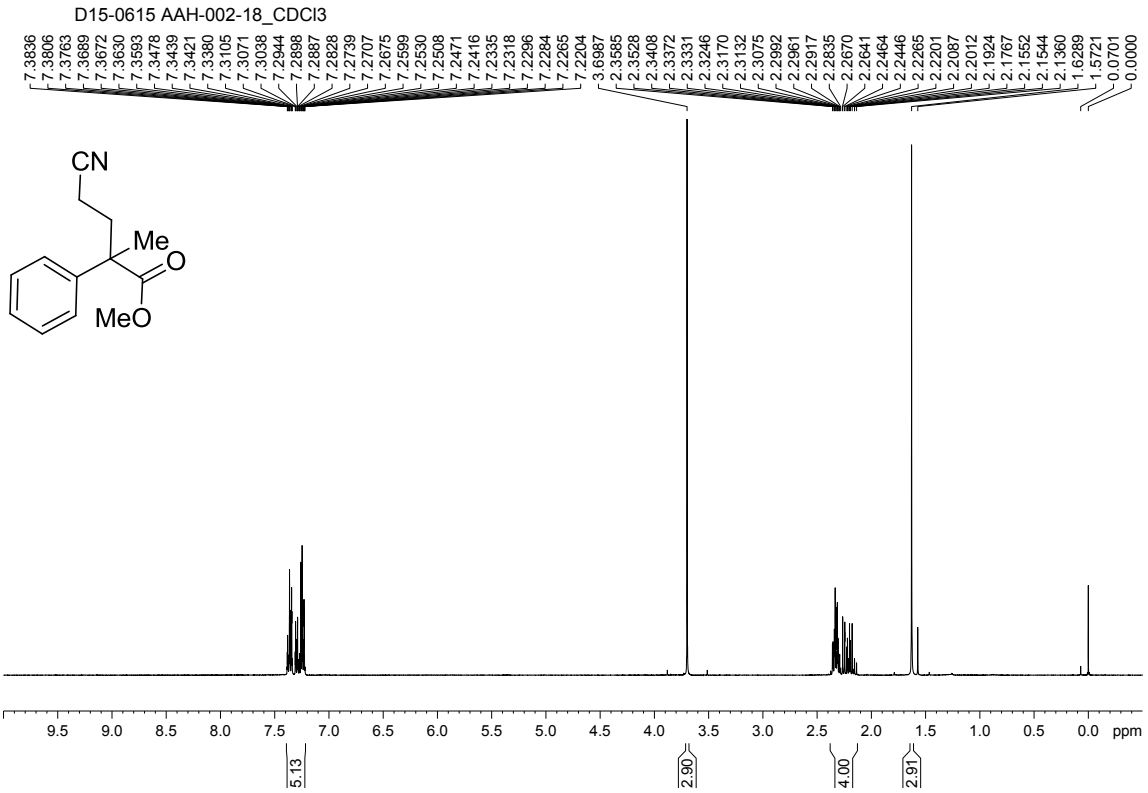
Appendix 14: 1,3-Bis(cinchonidinium-*N*-methyl)benzyl dibromide **172**

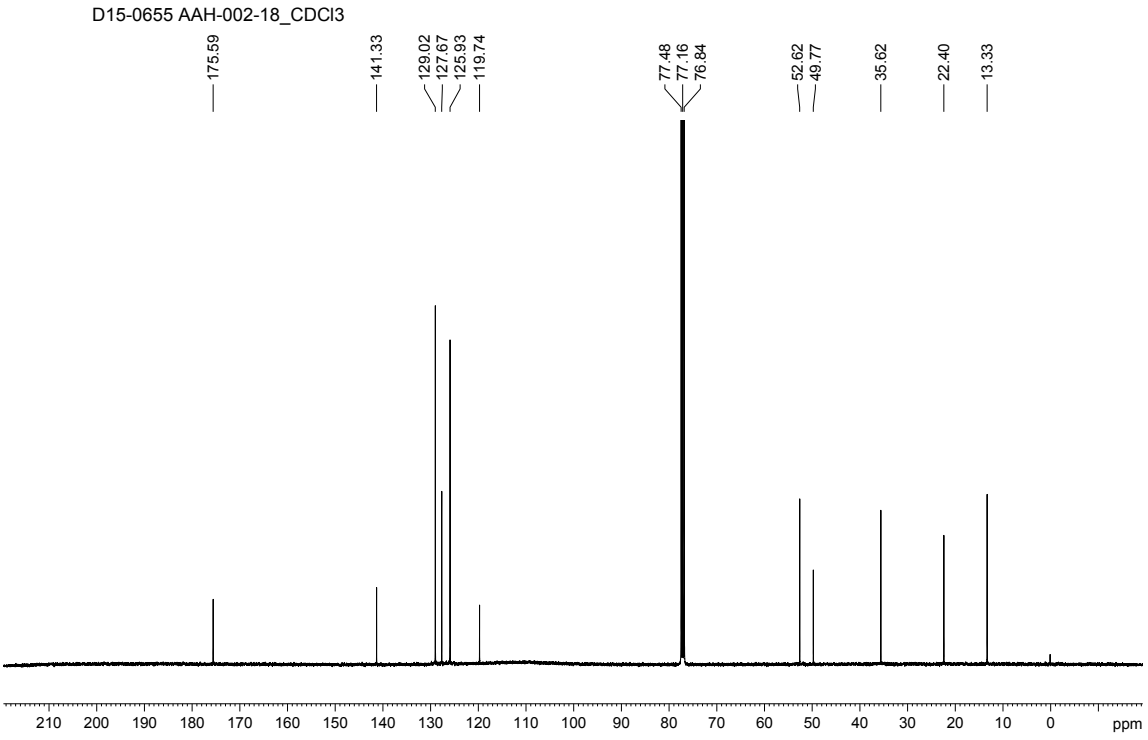
Appendix 15: 1,4-Bis(cinchonidinium-*N*-methyl)benzyl dibromide **173**

Appendix 16: Enantioselectivity method (HPLC)

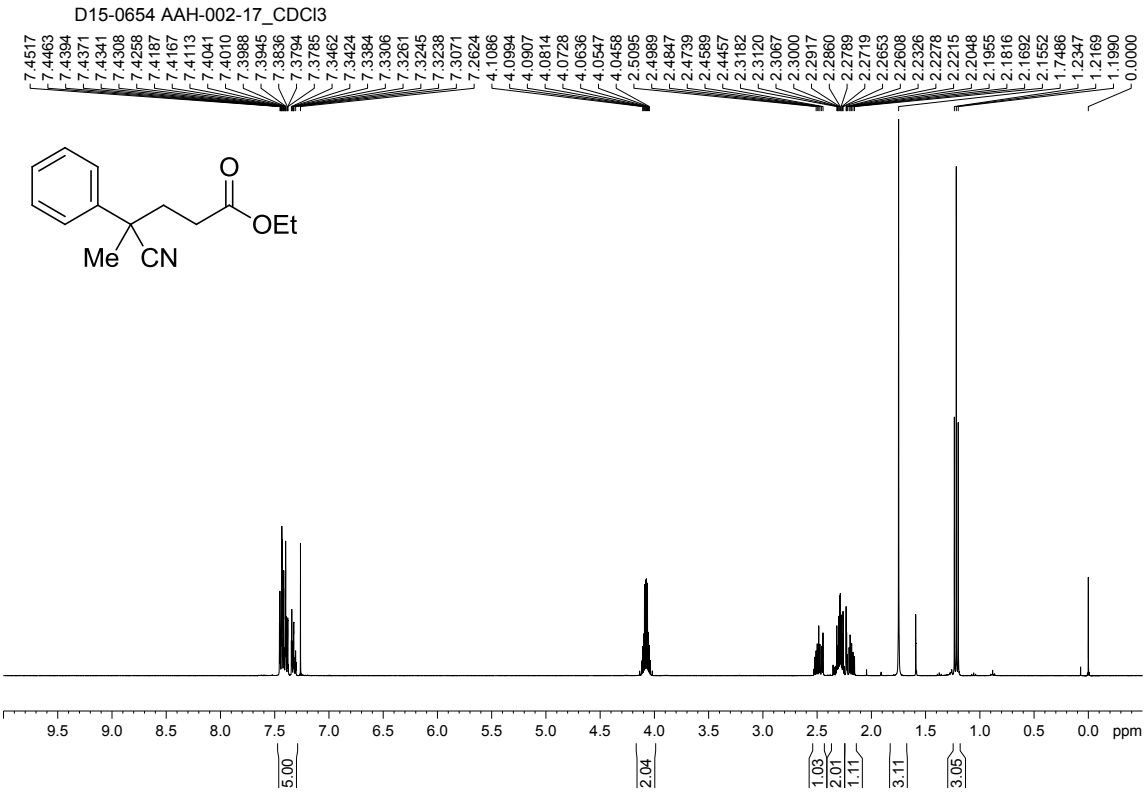
Appendix 17: Enantioselectivity method (UPC2 – supercritical CO_2)

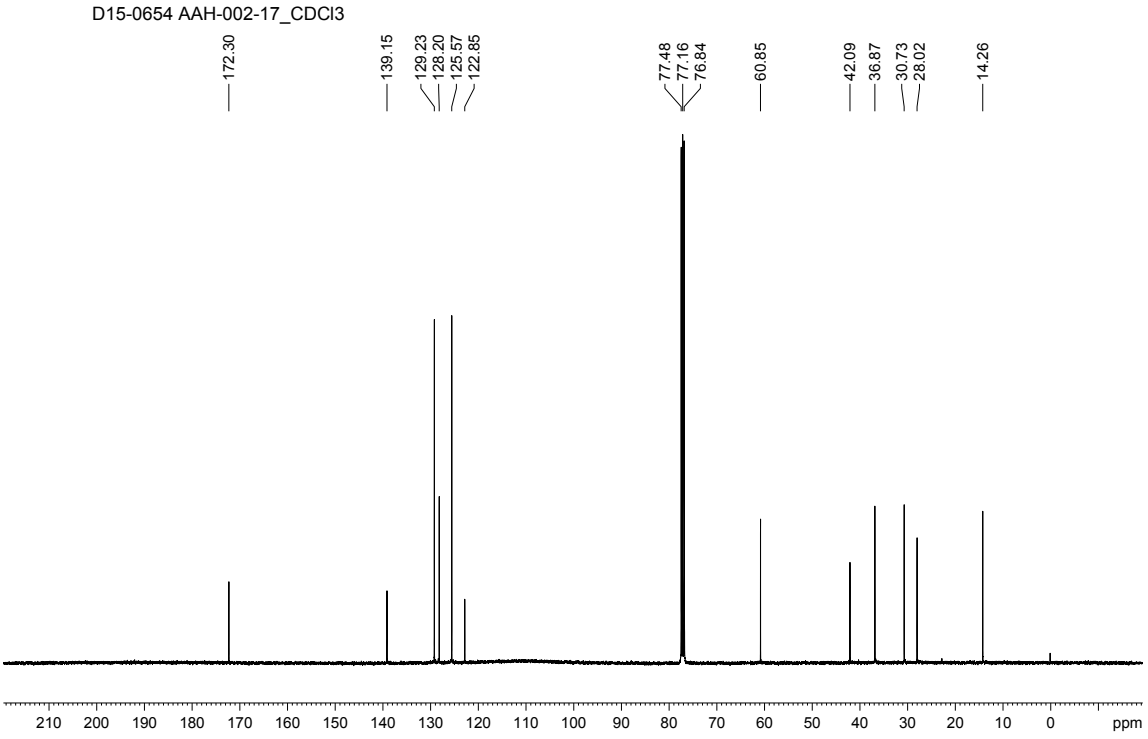
Appendix 1: Methyl 4-cyano-2-methyl-2-phenylbutanoate 159



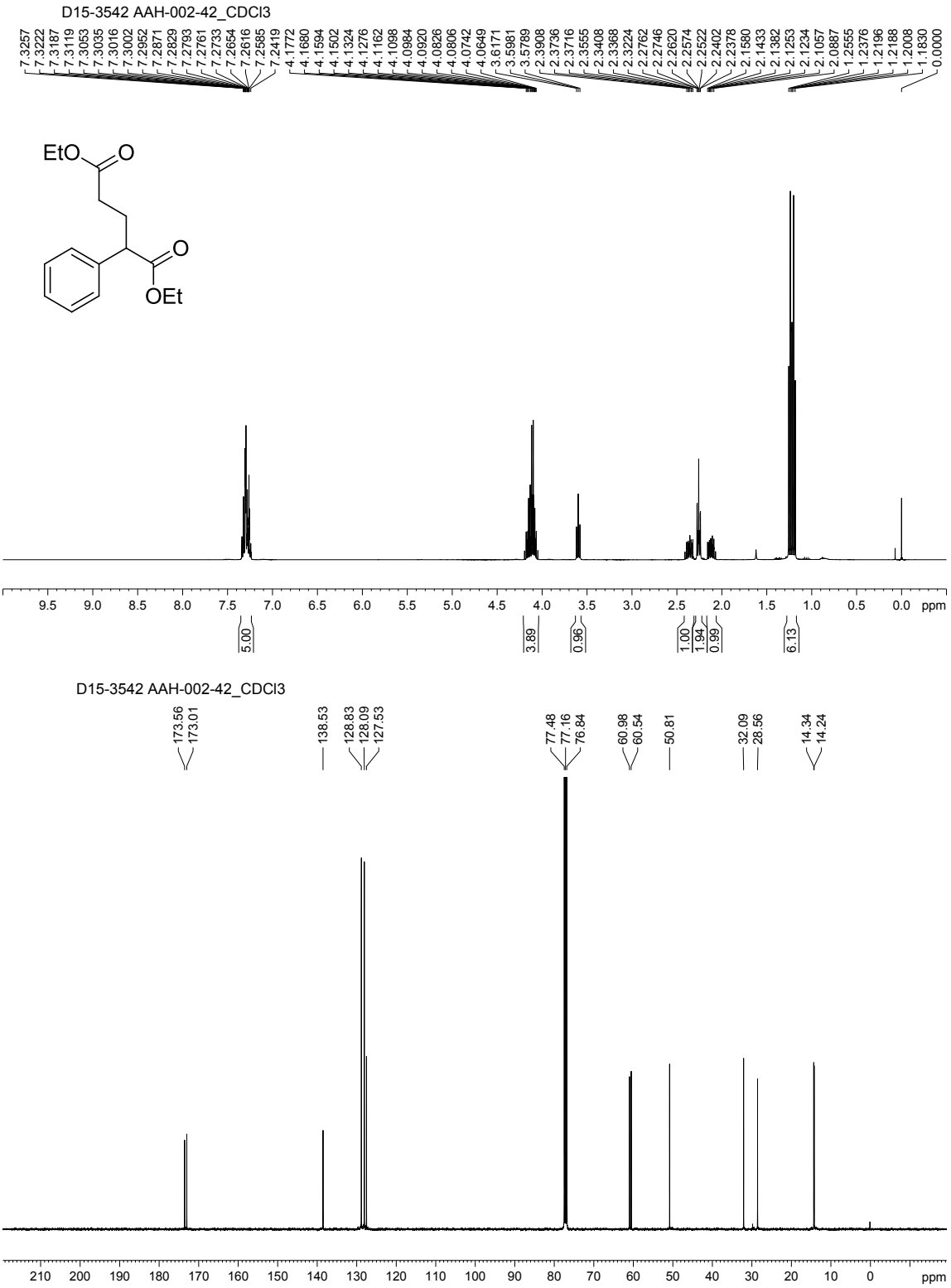


Appendix 2: Ethyl 4-cyano-4-phenylvalerate 177

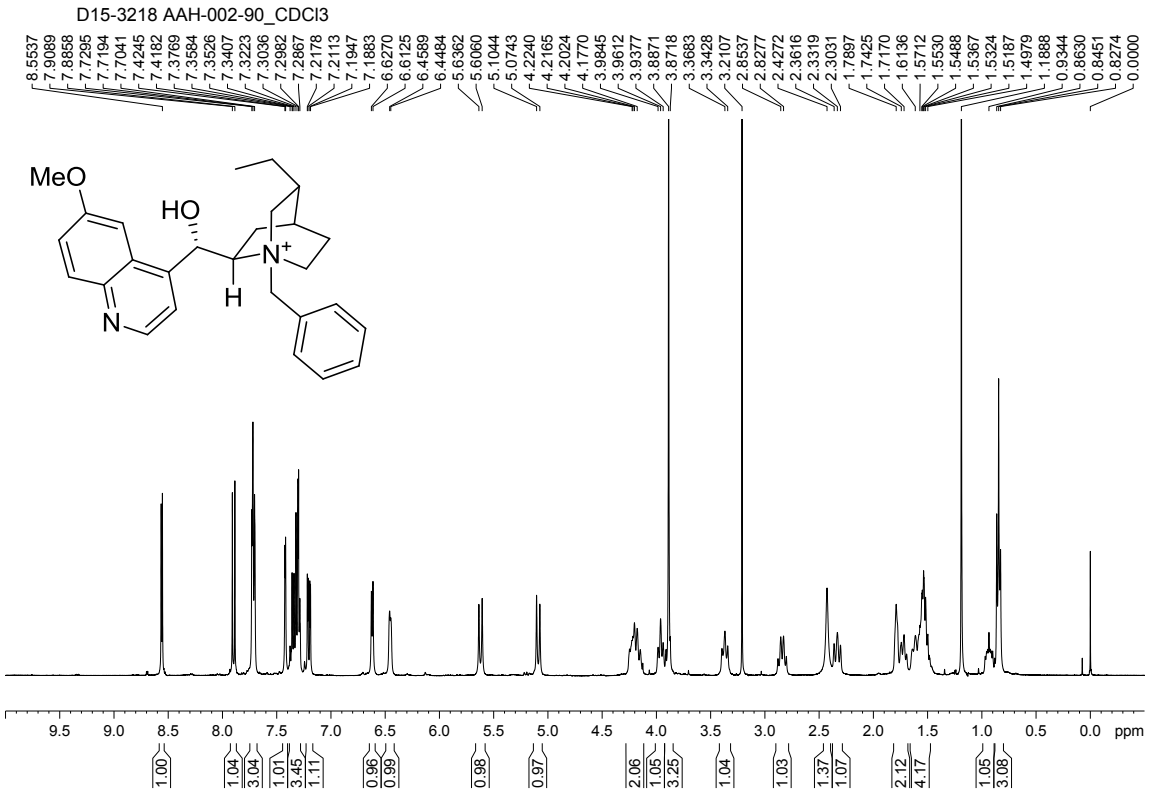


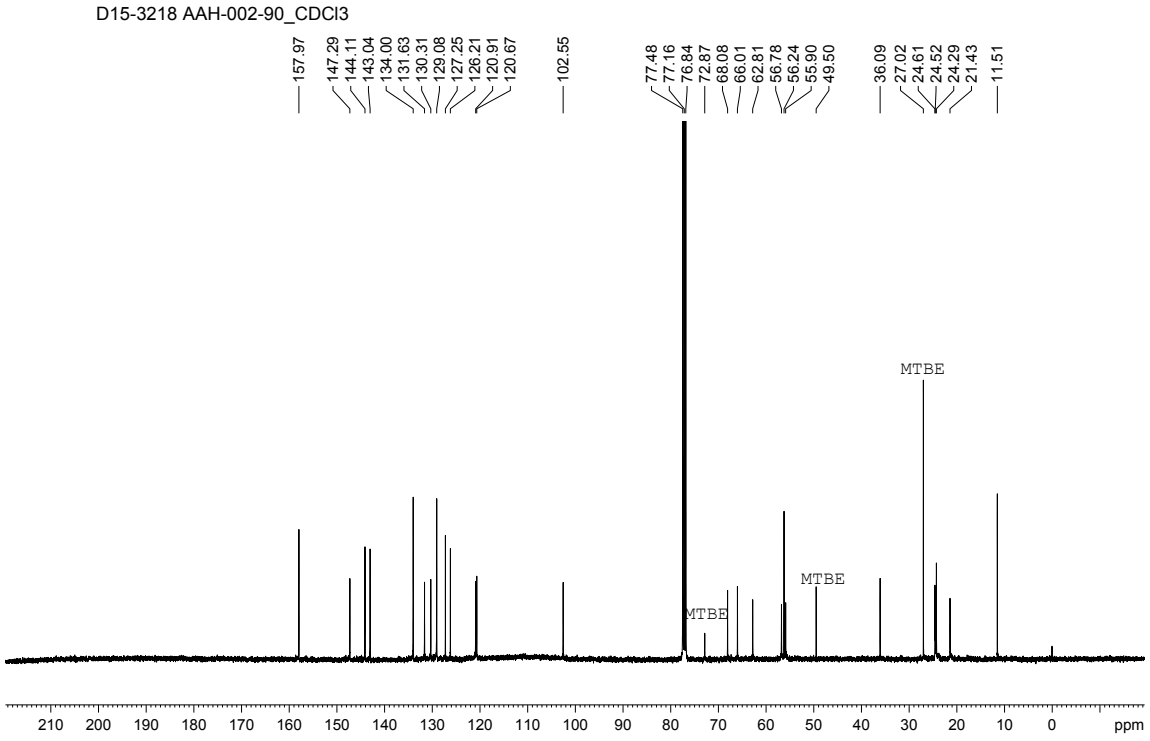


Appendix 3: Diethyl 2-phenylpentanedioate 181

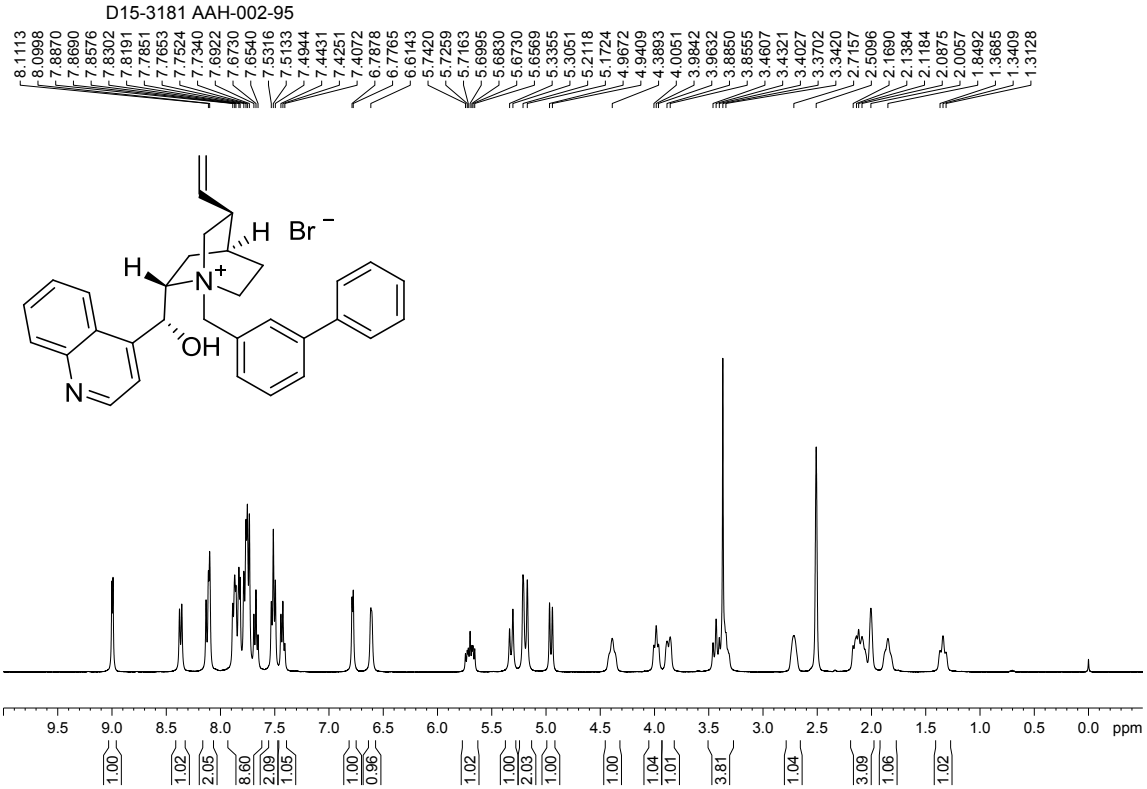


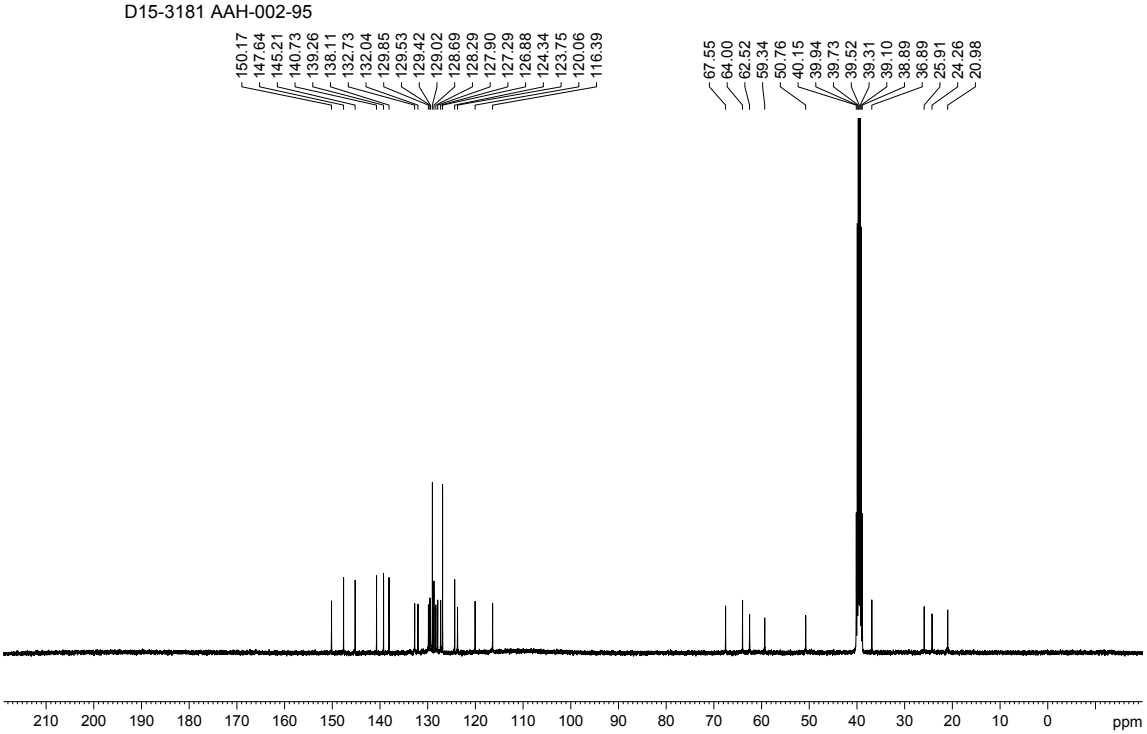
Appendix 4: *N*-benzyldehydroquinidinium bromide 162a



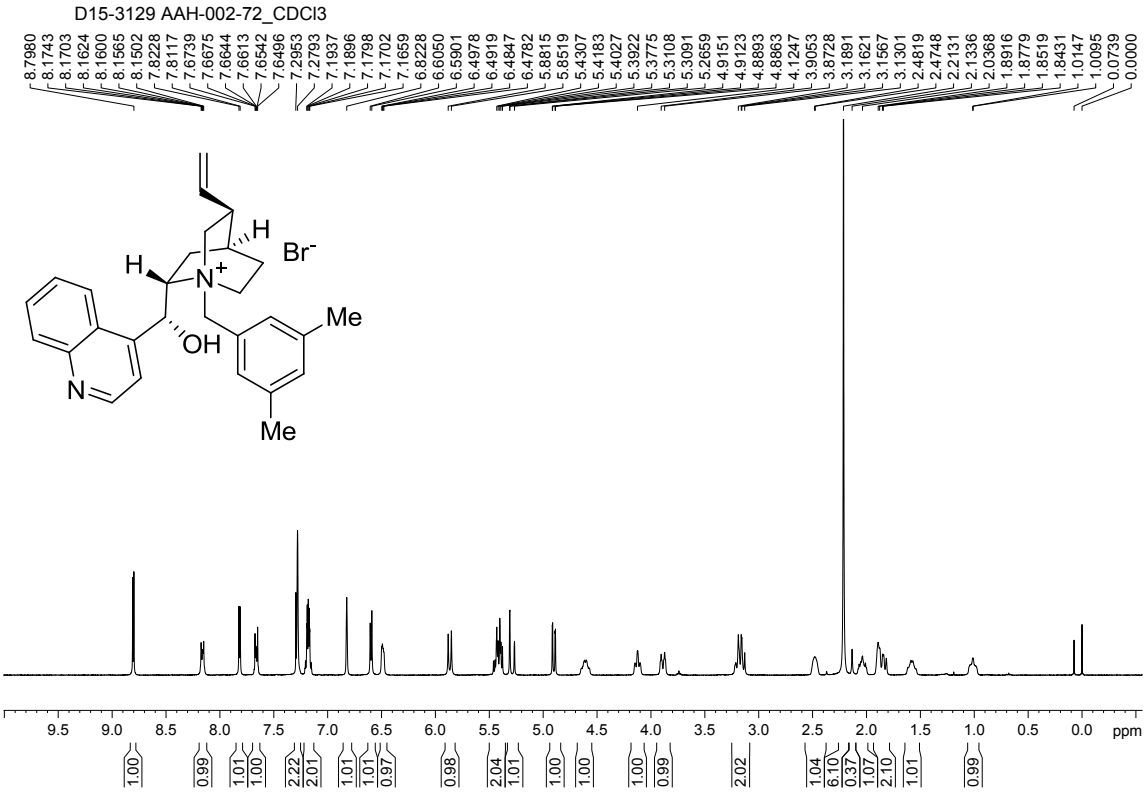


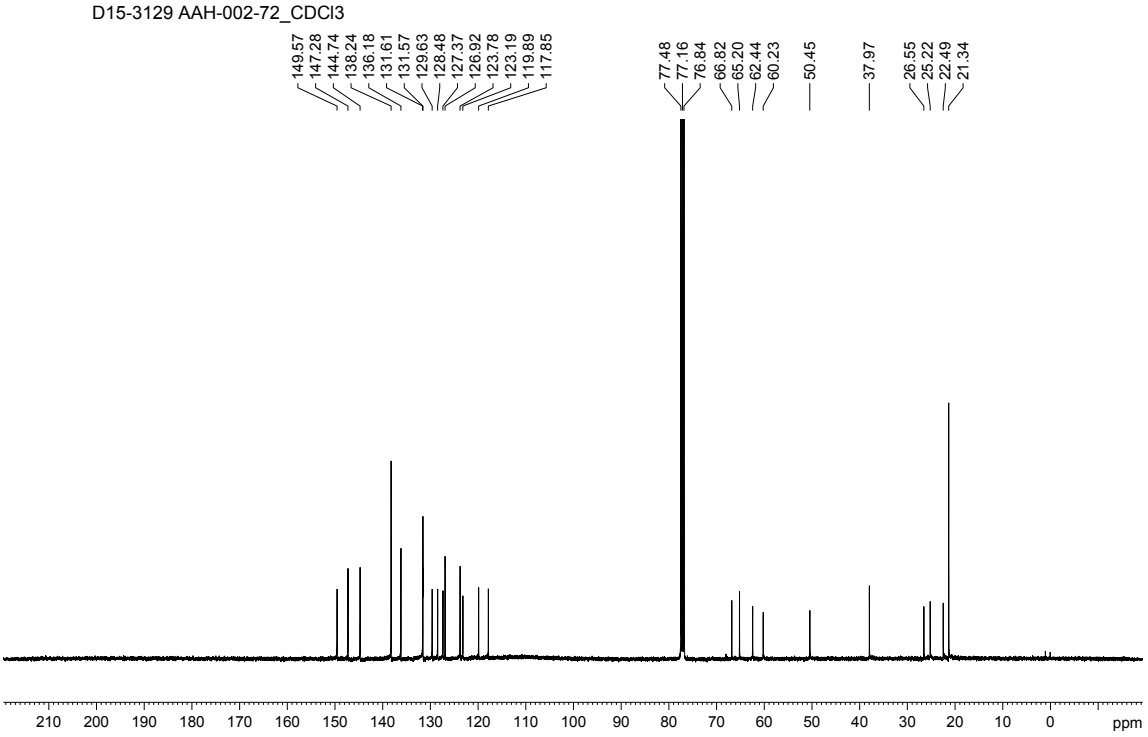
Appendix 5: *N*-(3-phenyl)benzylcinchonidinium bromide 163b



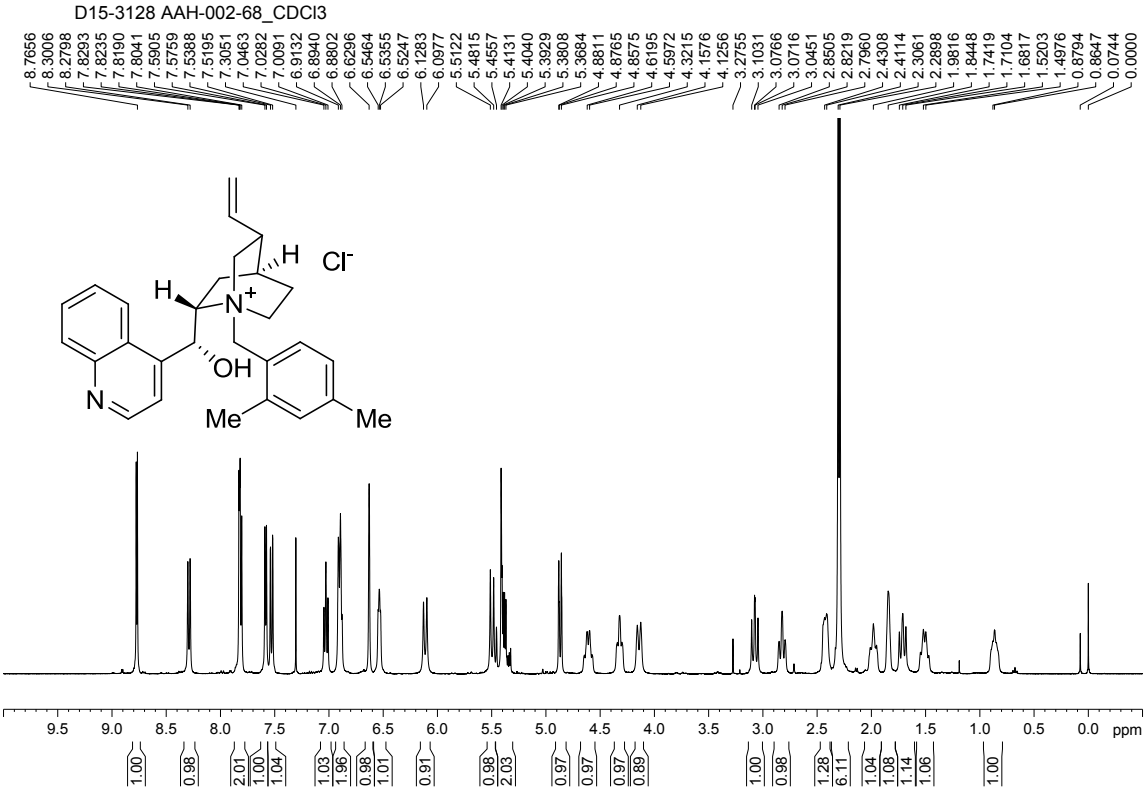


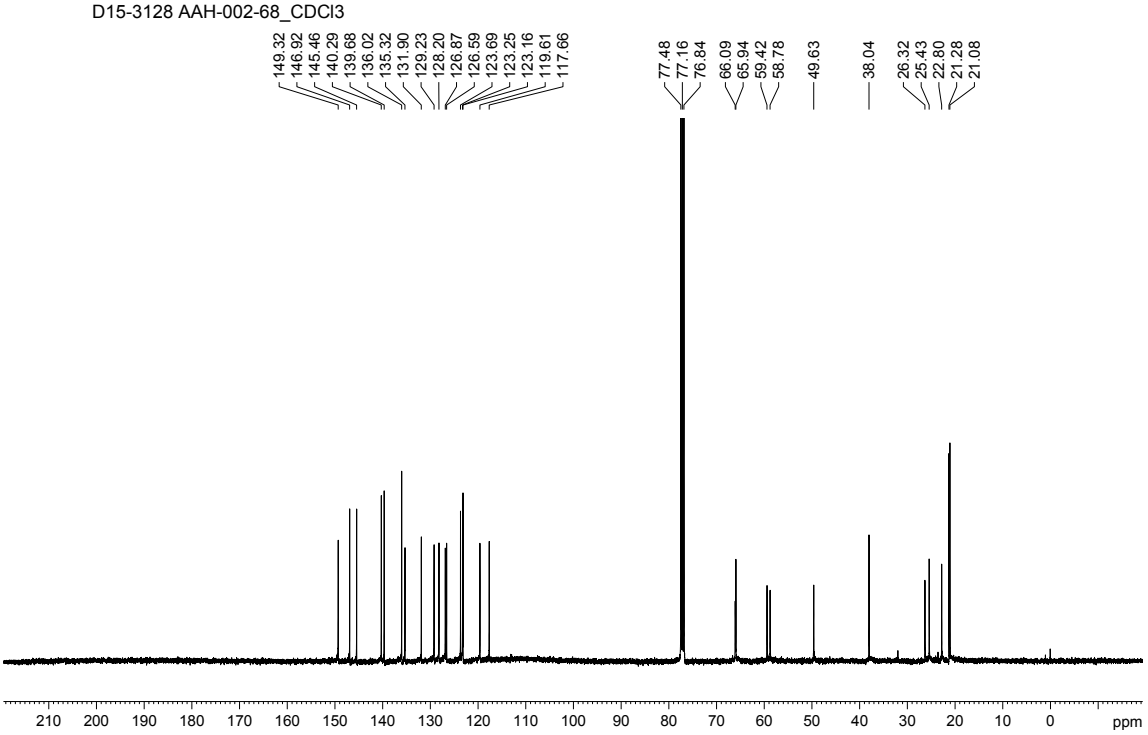
Appendix 6: *N*-(3,5-methyl)benzylcinchonidinium bromide 164b



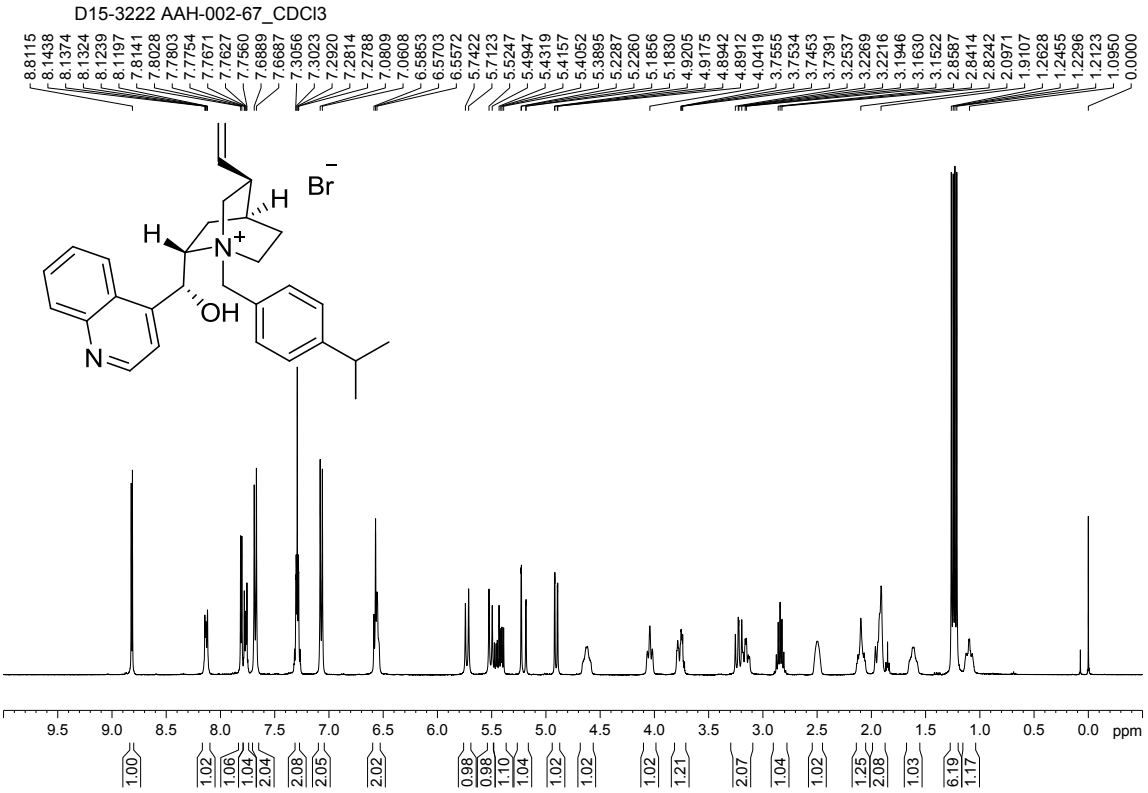


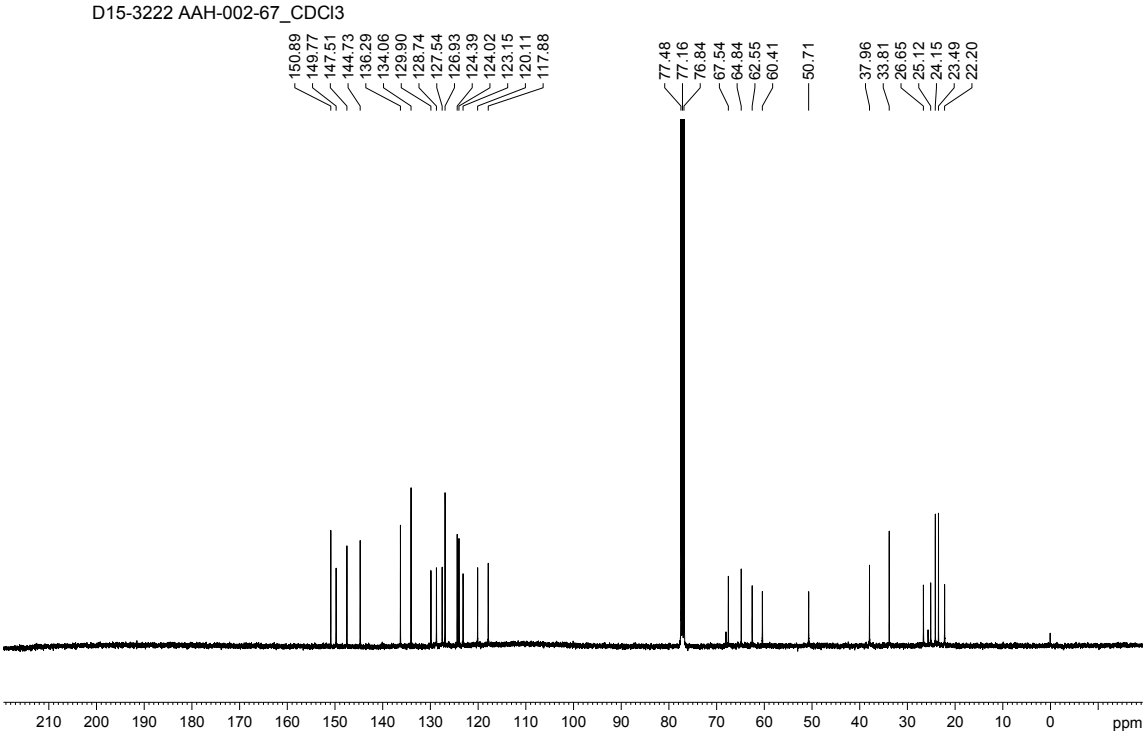
Appendix 7: *N*-(2,4-methyl)benzylcinchonidinium chloride 165b



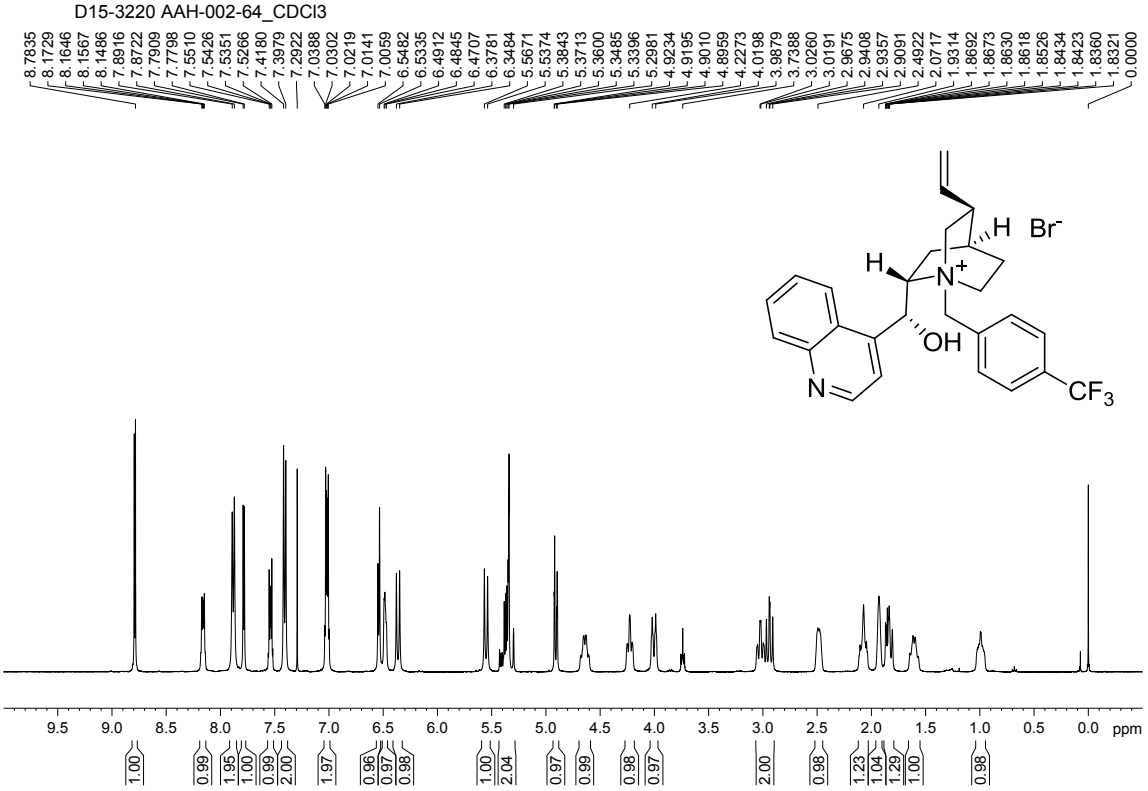


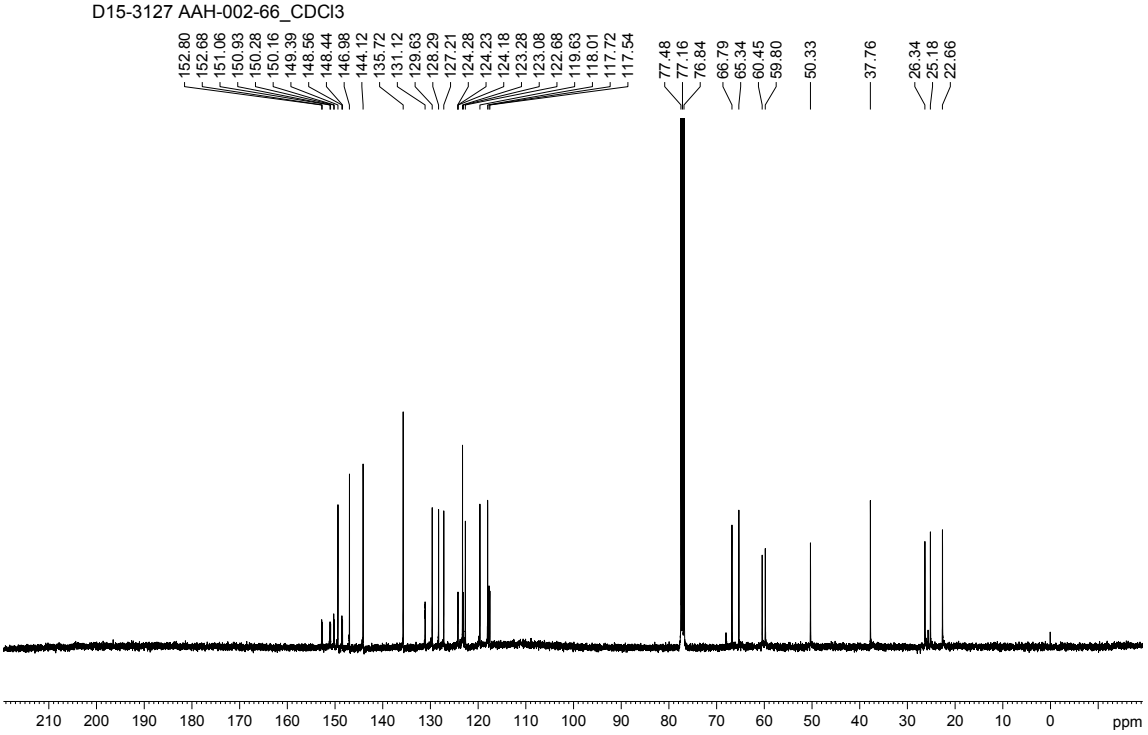
Appendix 8: *N*-(4-isopropyl)benzylcinchonidinium bromide 167b



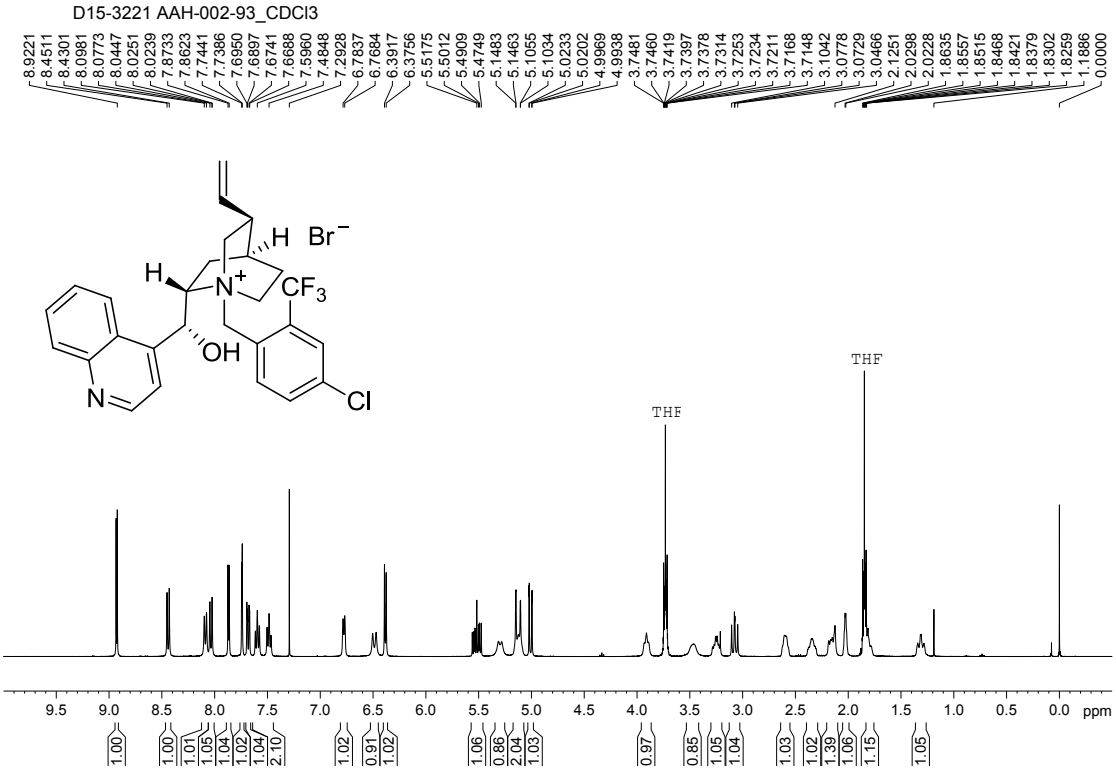


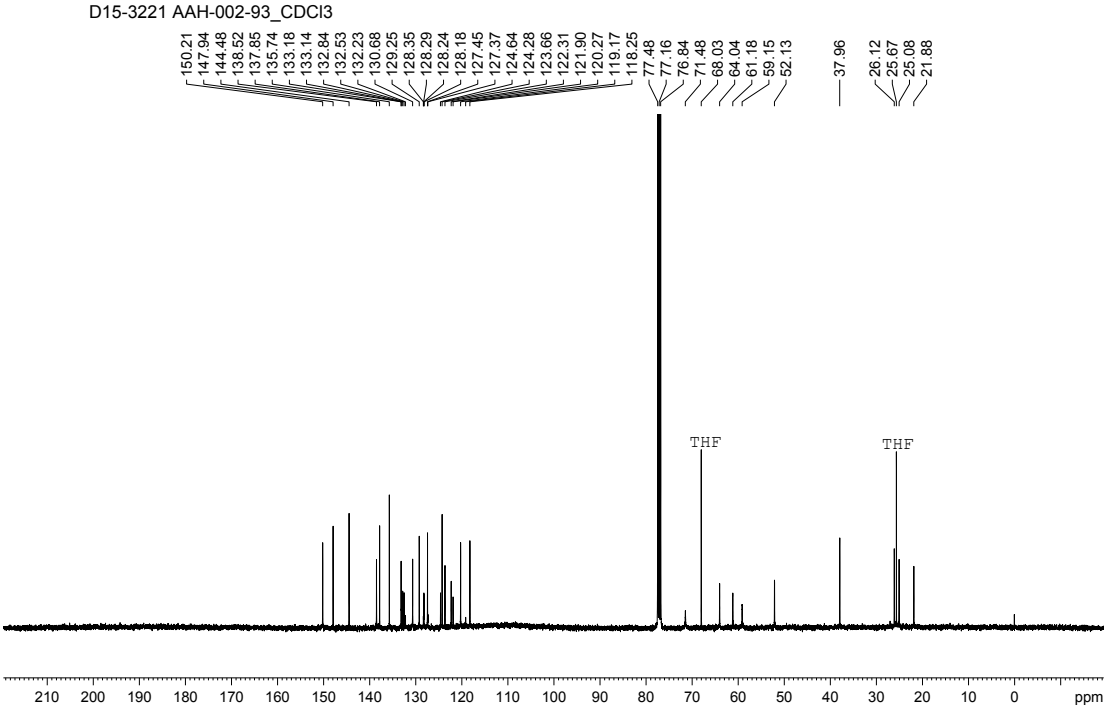
Appendix 9: *N*-(trifluoromethyl)benzylcinchonidium bromide 22b



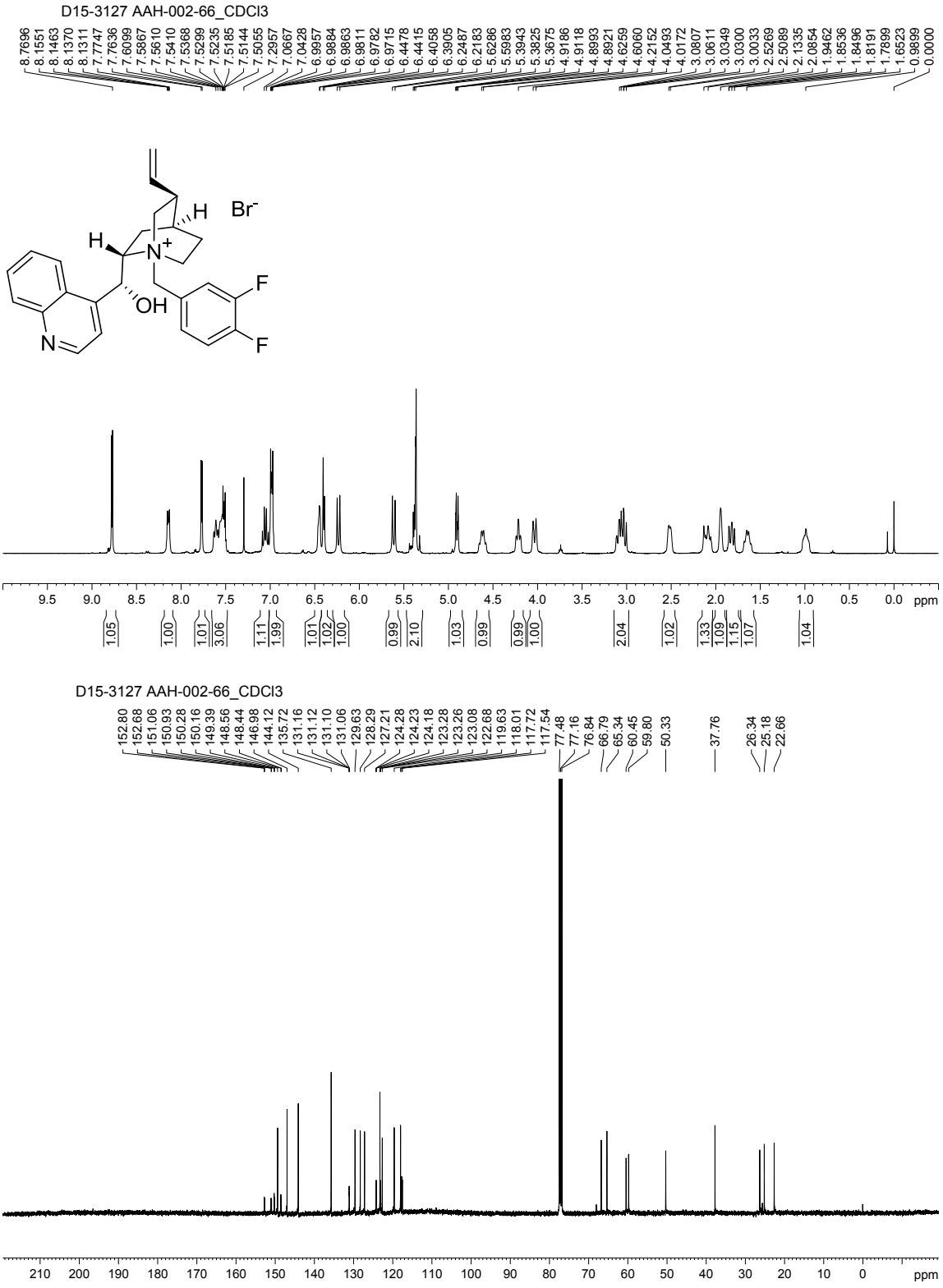


Appendix 10: *N*-(4-chloro-[2-trifluoromethyl])benzylcinchonidinium bromide 168b

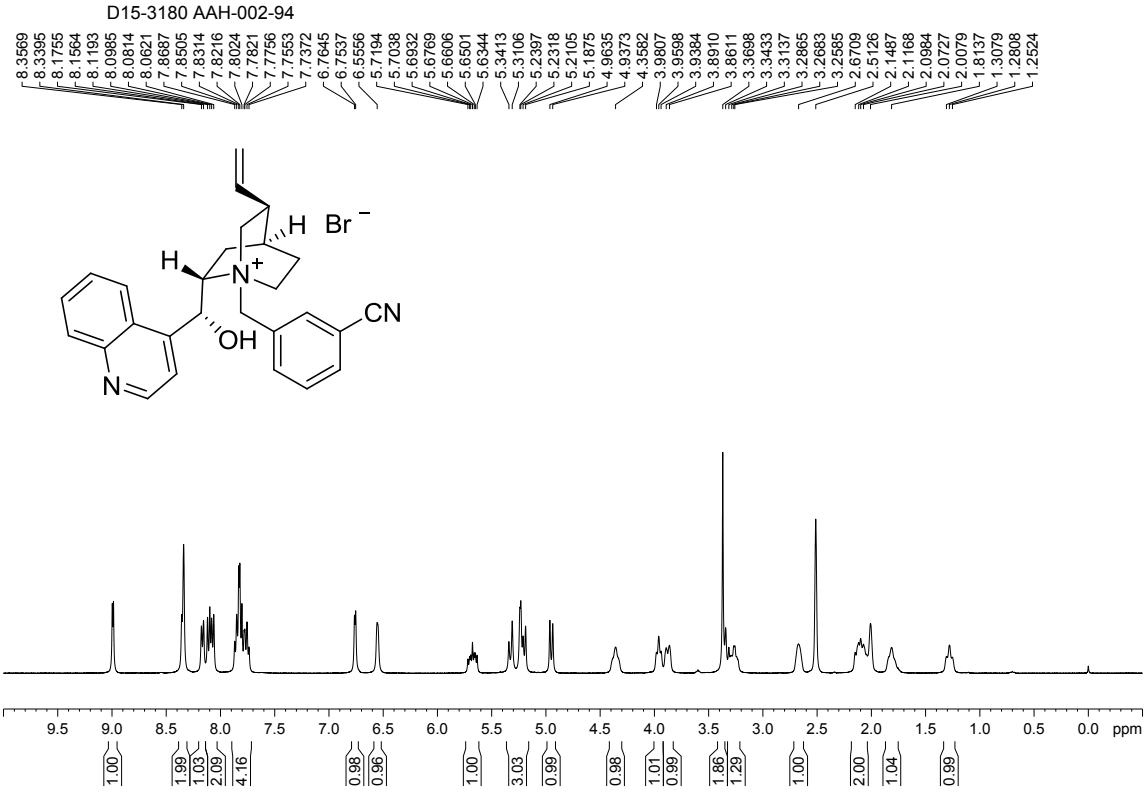


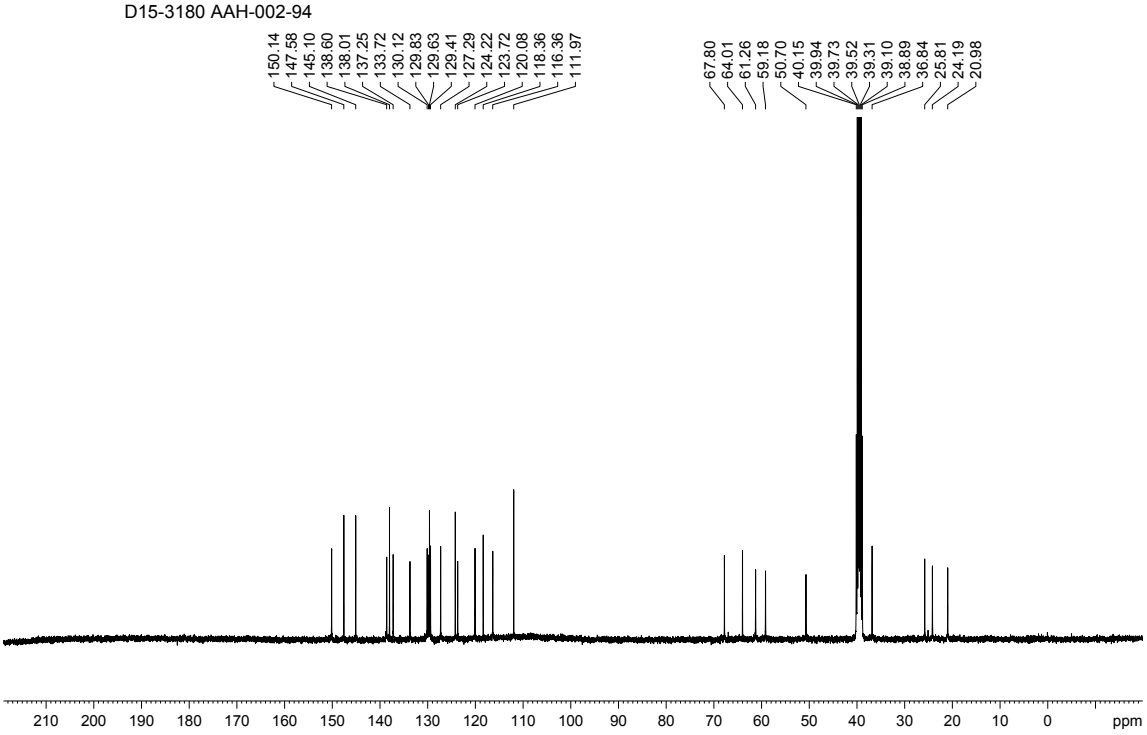


Appendix 11: *N*-(3,4-difluoro)benzylcinchonidinium bromide 169b

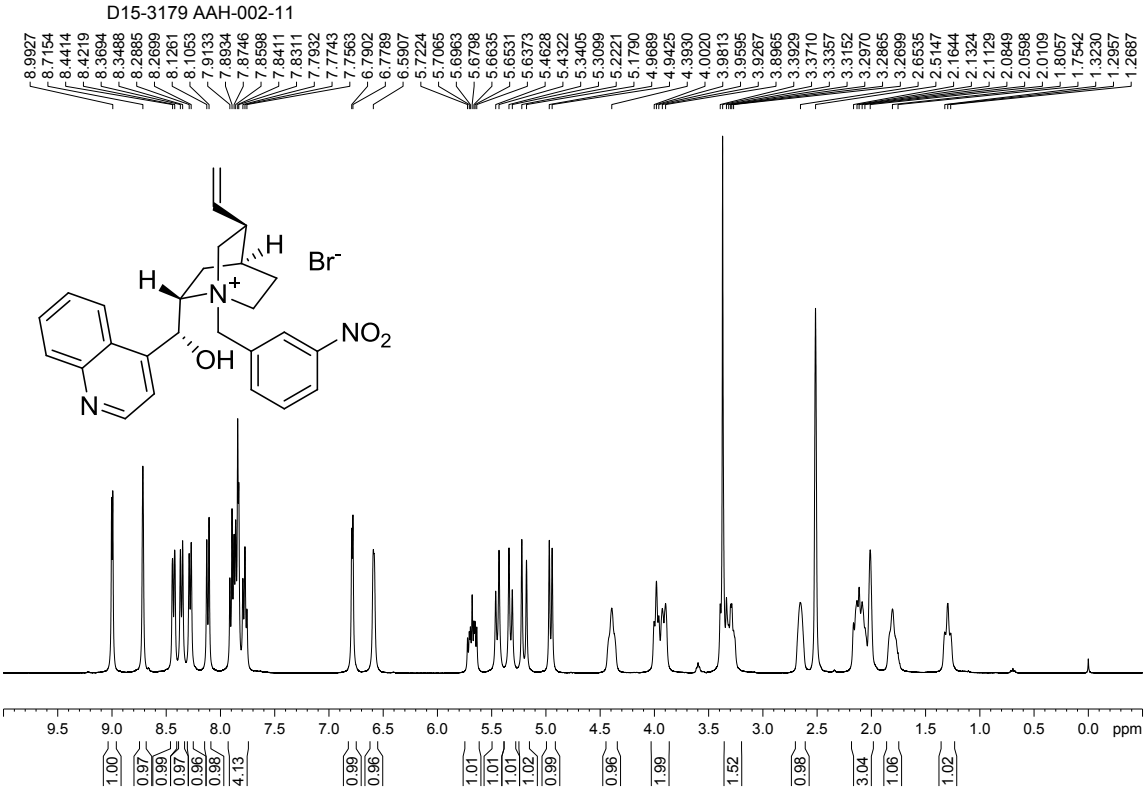


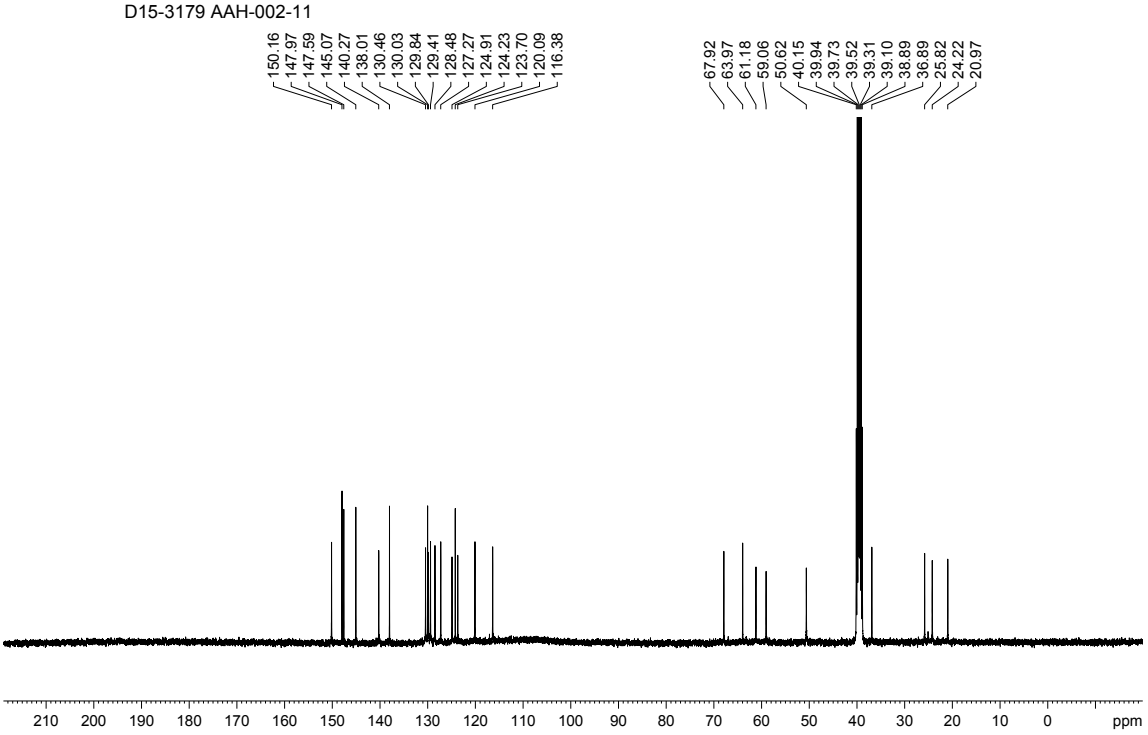
Appendix 12: *N*-(3-cyano)benzylcinchonidinium bromide 170b



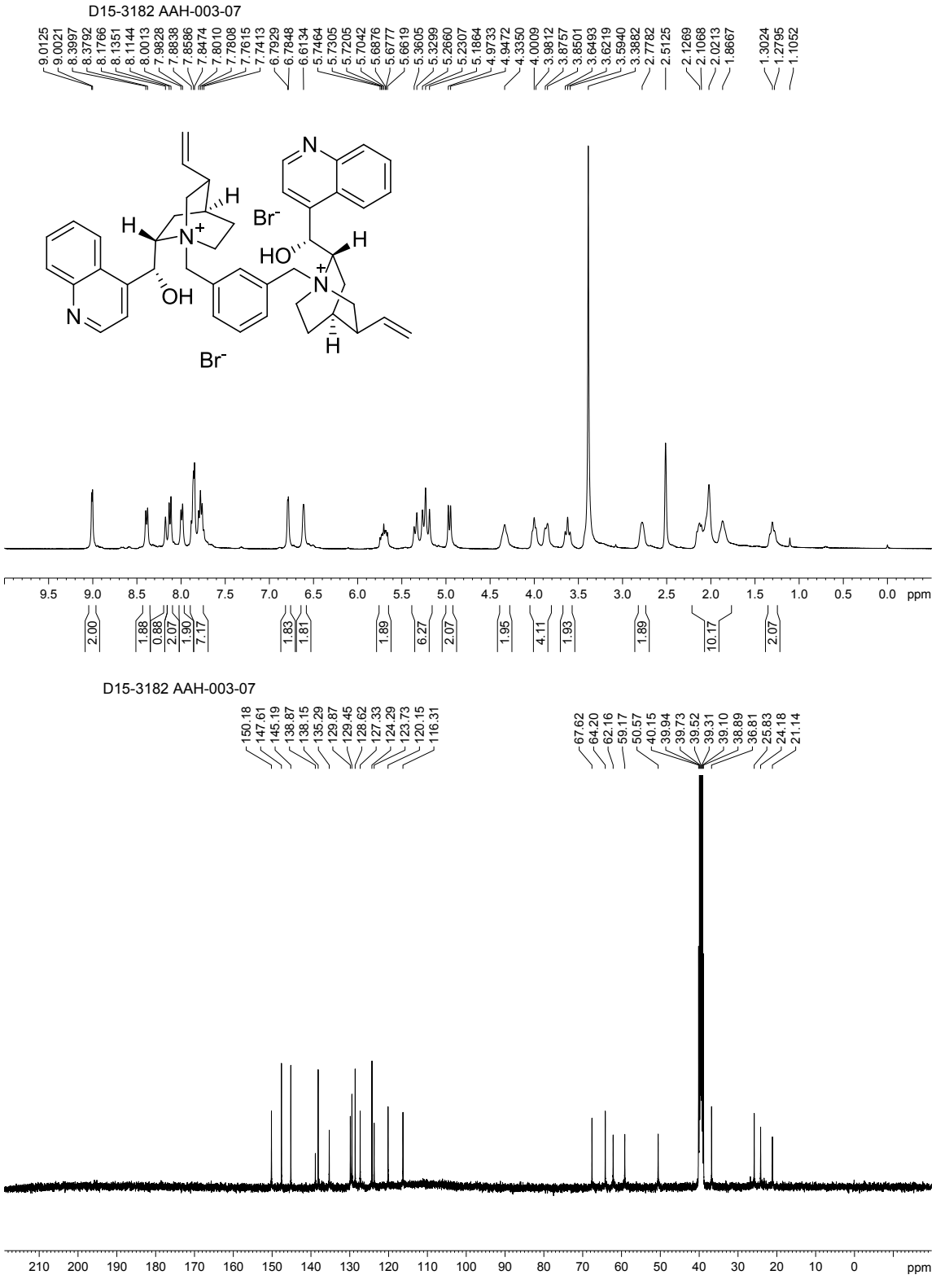


Appendix 13: *N*-(3-nitro)benzylcinchonidinium bromide 171b

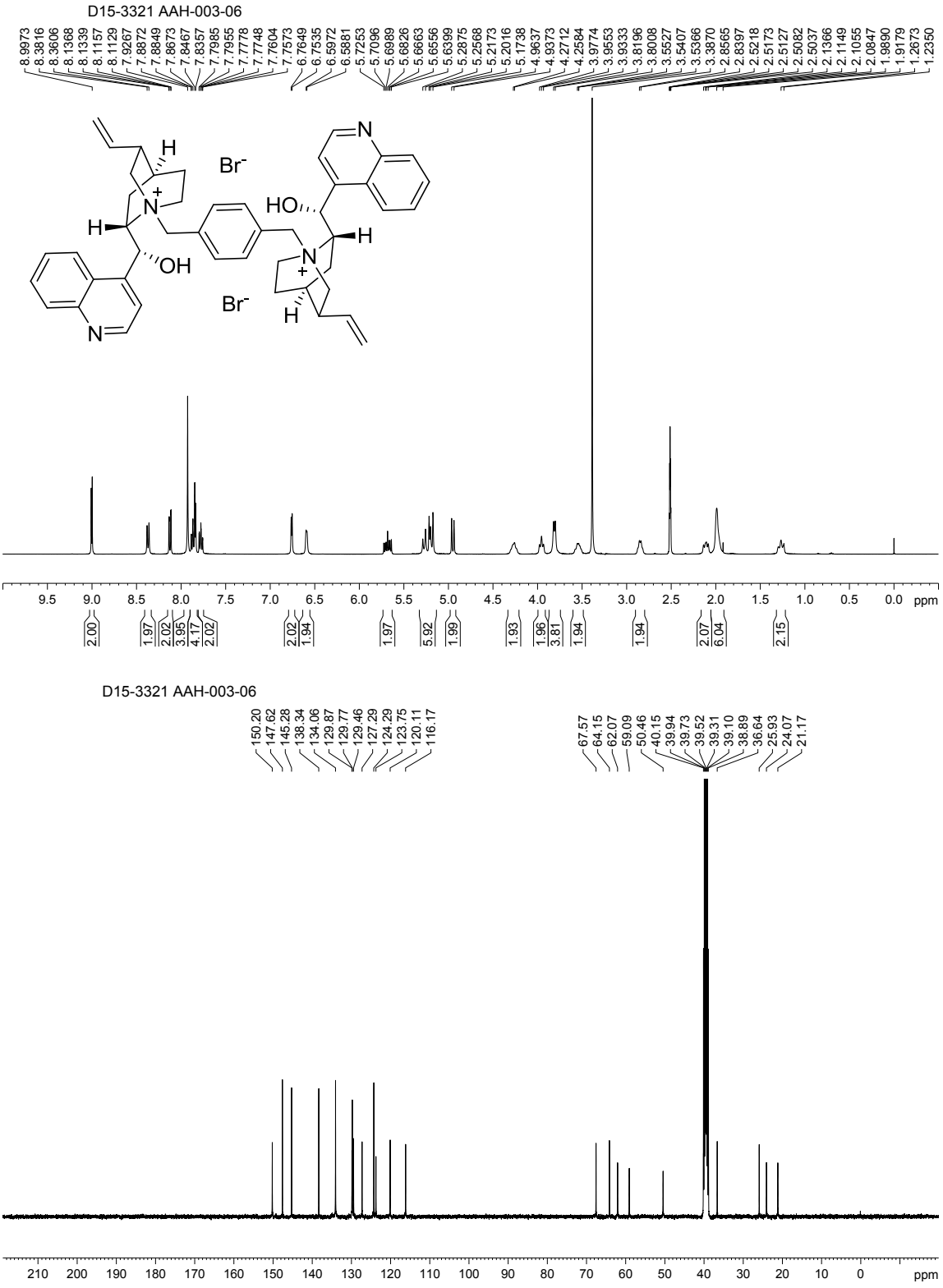




Appendix 14: 1,3-Bis(cinchonidinium-*N*-methyl)benzyl dibromide 172



Appendix 15: 1,4-Bis(cinchonidinium-*N*-methyl)benzyl dibromide 173

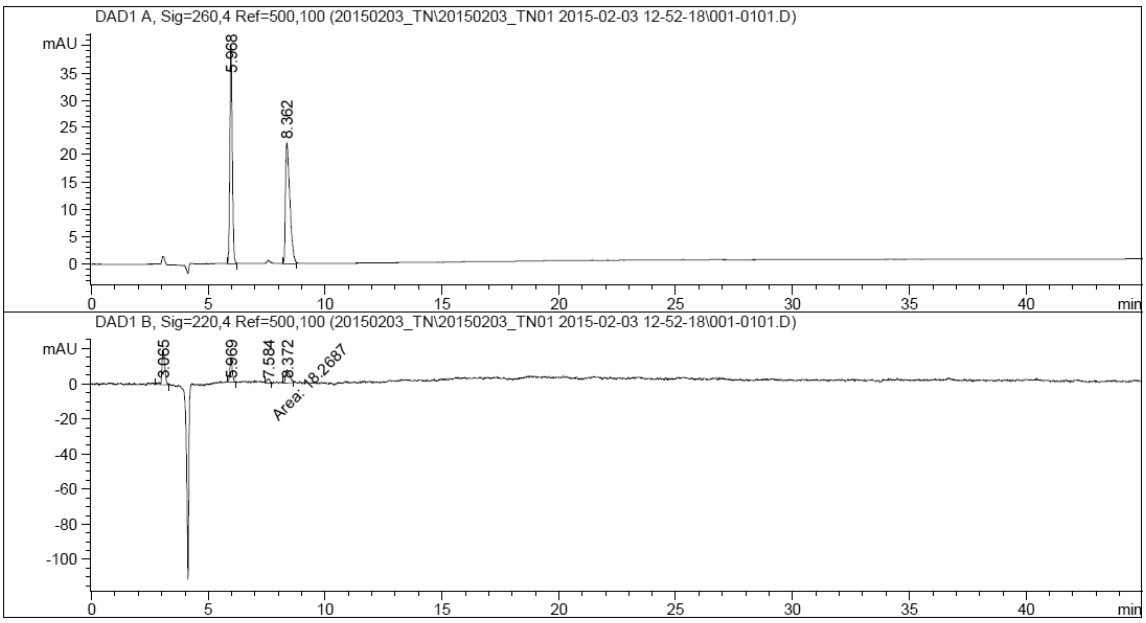


Appendix 16: Enantioselectivity method (HPLC)

Racemate:

```
Sample Info     : Optinen MEKE
                  AAH-002-17  n.4mg/ml EtOH

                  Chiralpak IA No 85
                  A1: n-Heksaani + 0.2 %DEA
                  B1: EtOH + 0.2 % DEA
                  B 10% , virtaus 1 ml/min., 260 ja 220nm
```



Signal 1: DAD1 A, Sig=260,4 Ref=500,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	5.968	BB	0.1081	282.15500	40.10557	49.9660
2	8.362	BB	0.1934	282.53876	22.06983	50.0340
Totals :				564.69376	62.17540	

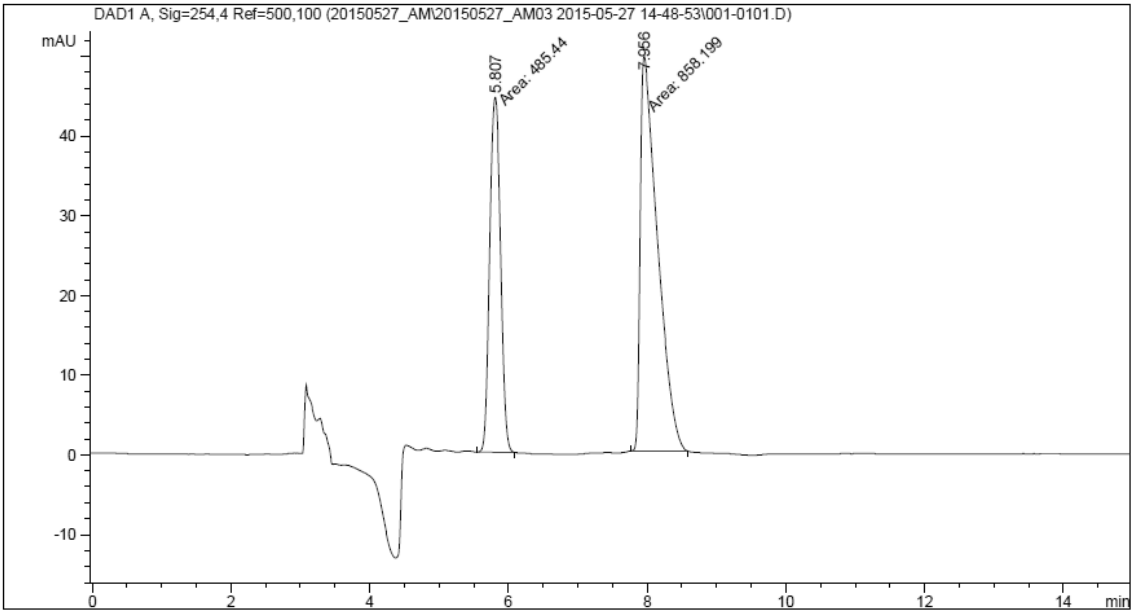
Signal 2: DAD1 B, Sig=220,4 Ref=500,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	3.065	BB	0.1320	165.35284	19.28459	43.8638
2	5.969	BB	0.1127	94.13416	12.97058	24.9714
3	7.584	MM	0.1375	18.26873	2.21410	4.8462
4	8.372	BB	0.1642	99.21272	7.60426	26.3186
Totals :				376.96844	42.07353	

Sample:

```
Sample Info     : Optinen puhtausanalyysi
                  AAH-003-02  n. 2mg/ml EtOH
                  Chiralpak IA no. 85 (Col1)
                  A1: n-heksaani + 0.2% DEA
                  B1: EtOH + 0.2% DEA
                  B10%, 1ml/min. 254nm, runtime 15min.

                  Chiralpak IA No 85
                  A1: n-Heksaani + 0.2 %DEA
                  B1: EtOH + 0.2 % DEA
                  B 10% , virtaus 1 ml/min., 260 ja 220nm
```

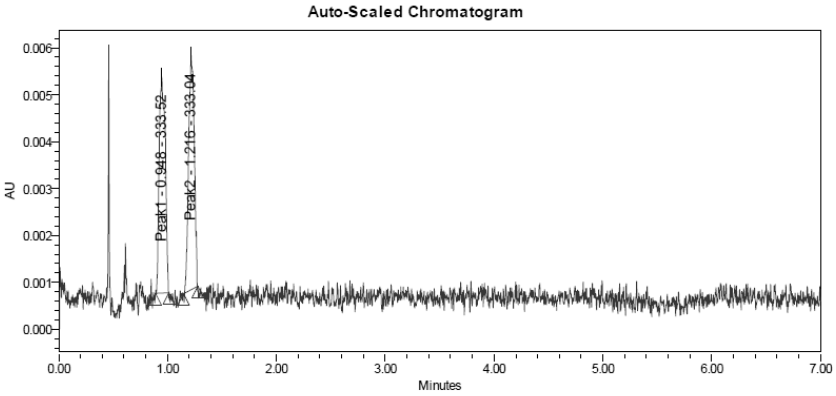


Signal 1: DAD1 A, Sig=254,4 Ref=500,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	5.807	MM	0.1815	485.43985	44.57901	36.1287
2	7.956	MM	0.2886	858.19934	49.55511	63.8713
Totals :				1343.63919	94.13411	

Appendix 17: Enantioselectivity method (UPC2 – supercritical CO_2)

Racemate:

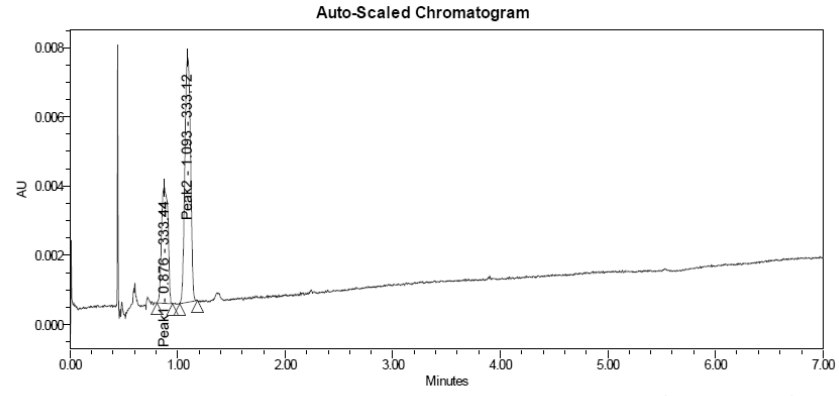


SampleName AAH_003_05_IRC_AMY1_1µl; Vial 1:B,4; Channel Name 255.0nm; Injection Id 1807; Result Id 1832; Sample_info n.2 mg/ml EtOH; Injection Volume 1.00; Modifier 0.1% DEA in IPA

Peak Results

	SampleName	Peak Name	Retention Time (min)	Height (µV)	Area (µV*sec)	% Area
1	AAH_003_05_IRC_AMY1_1µl	Peak1	0.948	4607	17834	49.54
2	AAH_003_05_IRC_AMY1_1µl	Peak2	1.216	4993	18165	50.46
3	AAH_003_05_IRC_AMY1_1µl	Peak3	4.028			

Sample:



SampleName AAH_003_01_IRC_AMY1_1µl; Vial 1:B,7; Channel Name 255.0nm; Injection Id 1843; Result Id 1864; Sample_info n.2 mg/ml EtOH; Injection Volume 1.00; Modifier 0.1% DEA in IPA

Peak Results

	SampleName	Peak Name	Retention Time (min)	Height (µV)	Area (µV*sec)	% Area
1	AAH_003_01_IRC_AMY1_1µl	Peak1	0.876	3348	13920	34.94
2	AAH_003_01_IRC_AMY1_1µl	Peak2	1.093	7074	25918	65.06
3	AAH_003_01_IRC_AMY1_1µl	Peak3	4.028			